THE JOURNAL OF EXPERIMENTAL MEDICINE

THE JOURNAL OF EXPERIMENTAL MEDICINE

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WITH FORTY-FOUR PLATES AND THREE FIGURES IN THE TEXT

NEW YORK
THE MACMILLAN COMPANY
LONDON: THE MACMILLAN CO., Ltd
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THE PRODUCTION OF SARCOSPORIDIOSIS IN THE MOUSE BY FEEDING INFECTED MUSCULAR TISSUE.

By THEOBALD SMITH, M. D.,

George Fabyan Professor of Comparative Pathology, Harvard University.

PLATES I–IV.

Since the discovery of sporozoan parasites belonging to the order now known as Sarcosporidia in the muscle fibres of the house mouse by Miescher in 1843, many other mammals and not a few birds have been found to harbor them. Some species, like the one described by Miescher, are quite conspicuous to the naked eye in the ultimate stage of development. Certain others, including those of swine, are microscopic. Those of cattle may be seen as barely visible, whitish specks when situated beneath the endocardium. Some of the species found in birds are fairly conspicuous as shown by the dimensions given by Stiles.[1]

The record of sarcosporidiosis in man is meagre and in part uncertain in value. Only two cases—one described by Kartulis[2] and one by Baraban and Saint-Remy[3]—seem to be genuine. In those of Lindemann[4] and Rosenberg[5] the diagnosis must remain doubtful. The case of Kartulis was that of a Sudanese. An abscess had formed in the liver and had extended to the abdominal wall. The sarcosporidia cysts were found in considerable numbers both in the liver and

[1] On the presence of Sarcosporidia in birds. Bulletin No. 3, p. 79, *Bureau of Animal Industry*, Washington, 1893.

[2] *Zeitschr. f. Hygiene*, 1893, xiii, p. 1.

[3] *Bibliographie anatomique*, 1894, p. 79; *Comptes rend. Soc. de biol.*, 1894, 10. s., i, p. 201.

[4] From the Russian in *Deutsche Zeitschr. f. Staatsarzneikunde*, 1868, n. F., xxvi, p. 326.

[5] *Zeitschr. f. Hygiene*, 1892, xi, p. 435.

the muscular tissue forming the periphery of the abscess.[6] Baraban and Saint-Remy found genuine sarcosporidia cysts in the muscular fibres of the vocal cords of an executed criminal. The cysts, from .077 mm. to .168 mm. in diameter, were chambered and each chamber was filled with falciform bodies or sporozoites. These two cases indicate that some one or more of the muscle parasites of the lower animals may reach maturity in the human subject.

This brief epitome of sarcosporidiosis in man leaves to this subject but little that is of immediate practical importance to human pathology. It should not be forgotten, however, that the muscular system in man is not subjected to that scrutiny which the viscera undergo in pathological enquiries and that Sarcosporidia may be present and yet not be recognized. As in trichinosis, the invasion may be overlooked or the attending symptoms misinterpreted and the subsequent quiescent stage fail to arouse any attention. The fact that the etiology of acute primary polymyositis is still unsettled should lead to more careful examination of the muscular system as a part of routine pathological work. It is not improbable that invasion of the muscular system by aberrant parasites may take place now and then. Such parasites being in the wrong host may fail to develop and hence elude detection, while the products resulting from their disintegration may lead to inflammatory reaction.

The supposition that Sarcosporidia are transmitted by way of the digestive tract has been a favorite hypothesis of investigators and has been frequently tested by feeding infected muscle. No positive results have been reported. The failures were, no doubt, in part at least, due to the method of experimentation. The endeavor to transmit Sarcosporidia of sheep by injecting them into white mice and guinea-pigs as was done by Kasparek,[7] or by the eating of raw meat by human beings as was done by Moulé,[8] seems at best abortive, since

[6] Max Braun in reviewing this case did not hesitate to regard the diagnosis of Sarcosporidiosis as extremely doubtful, but he subsequently fully agreed with Kartulis after having examined the latter's preparations (*Centralbl. f. Bakteriol.*, 1895, xviii, p. 13).

[7] *Centralbl. f. Bakter.*, 1895, xviii, p. 327.

[8] Des sarcosporidies et de leur fréquence, principalement chez les animaux de boucherie. Paris, 1887.

these parasites are highly specialized forms. It is a priori not improbable that the same species of Sarcosporidia may infect several hosts possessing certain, to us unknown, relationships, but to gain an insight into the life history of such forms the problem first to be solved is to determine the mode of transmission in the same species in which they naturally occur.

The negative results of recorded transmission experiments, to which we may safely add many unpublished ones, induced me to make an effort to fill at least a portion of the existing gap when, in 1898, I found a large proportion of gray mice which had been kept in a large wooden cage for over a year infected with Sarcosporidia. The large number of infections suggested that transmission occurred directly and not through an intermediate host. The occasional discovery of dead mice in this cage, of which parts had been consumed, as well as the not infrequent mutilation of the tails and scrota of living mice, led to the hypothesis referred to above that the infection takes place through the digestive tract in a manner analogous to the transmission of Trichinæ. Though the experiments needed to demonstrate the truth or falsity of this hypothesis seemed at first simple and easily executed, yet in the course of carrying them out a number of factors appeared which had to be taken into account. The length of time consumed by each feeding experiment, about 3 months, permitted the introduction of the new control factors only slowly, so that these tests have extended over a period of more than 2 years.

In order to present the more important facts of these investigations in an intelligible manner, I shall first relate the life history of the muscle parasite as interpreted by the results obtained. I shall then give such details of the actual experiments as may be necessary to enable others to estimate their relative value in establishing the results claimed and to repeat them if thought desirable.

Sarcocystis muris (R. Blanchard) Labbé.[9]

(*Miescheria muris*, R. Blanchard, 1885.)

The parasite, as a rule, is noticed only in its matured state when it becomes visible to the naked eye. It seems to be pretty widely dis-

[9] *Das Tierreich. Sporozoa*, p. 119. Berlin, 1899.

seminated and infected mice are encountered at intervals in most laboratories where mice are kept, to judge from verbal accounts of such discoveries in this country. The frequency with which they are found in rooms whither mice are drawn by ample food supply and where they breed is discussed in a subsequent section of this paper.

A mouse whose muscular system contains matured parasites presents a very striking appearance. If the skin be removed all the skeletal muscles will be seen to contain streaks of a whitish color. These may be so numerous as to leave but little of the normal red color of the muscle or they may be quite scarce (Plate IV, Fig. 7). Even the muscles of the head and the diaphragm are invaded. I have found them in sections of the eye muscles. The heart muscle, however, remains free. These linear streaks run parallel to the muscle fibres. In case of superimposed translucent layers whose fibres run in different directions, as in the abdominal muscles, the streaks are seen crossing one another at different angles. They vary more or less in length, the oldest and largest being from 1 to 1.5 cm. long and about .25 mm. broad. The more isolated ones are of greater width than those crowded together.[10]

If a piece of fresh muscle be teased in some indifferent fluid and examined under a low power the whitish streaks resolve themselves into opaque, thin-walled tubes, densely packed with crescentic bodies, the so-called sporozoites.[11] The outer wall of such a tube is very thin, smooth, and without any external appendages. It is usually encased by a narrow rim of muscle fibrillæ, the remains of the invaded fibre. Within this parasitic tube, among the sporozoites, a faint network of lines is discernible which forms flattened meshes whose long axes are at right angles to that of the parasite itself. These are

[10] According to investigations made by Mrs. Gage (*The Microscope*, 1888, viii, p. 225) some of the fibres in the shorter muscles of the mouse extend from tendon to tendon. In the longer muscles they are as a rule shorter than the muscle itself. Exact measurements of isolated fibres showed a variation in length of from 5 mm. in the short muscles to 22 mm. in the longest muscles. I have not made any measurements upon isolated infected fibres, but all observations point to the inference that the parasite eventually occupies the entire length of the muscle fibre in which it happens to lodge.

[11] The terminology used in this article is that suggested by Schaudinn (see Lühe's review in *Centralbl. f. Bakt.*, 1900, xxvii, p. 367).

optical sections of partitions which divide the entire parasite into chambers which enclose the sporozoites (Plate I, Fig. 1). When the parasite is torn by teasing, the latter escape and are found isolated (Plate III, Fig. 5). In outline they are crescentic and resemble bananas. The body in the middle is .004 mm. thick and measures in a straight line from end to end .012 mm. A modicum of fine granules is recognizable but nothing more.

When these sporozoites, suspended in normal salt solution, are warmed to 35° or 37° C. they exhibit peculiar movements. These are better observed in slide cells with convex bottom than in the hanging drop. By melting down the corners of square cover-glasses, as recommended by Siedlecki, good cells may be improvised with ordinary slides. The cells must be sealed with vaseline to prevent the concentration of the salt solution. The observations are most satisfactorily made with the aid of a Nuttall thermostat into which the entire microscope is placed.

It will be noticed as the temperature rises that these bodies have become more homogeneous and somewhat refractive and that their form has become slightly altered. They are now more curved and somewhat more slender. At 34° to 36° C. they begin to move in a gliding manner on a circumference corresponding to their own curvature for from 1½ to 2 revolutions. Then they suddenly flop over, *i. e.*, revolve on their long axis ¼ to ½ a revolution. After from 15 to 30 seconds of rest they pass through the same motions anew. Flagella were not observed. These movements may be observed for several hours. During the second hour they grew less and less vigorous, and finally only a few remained active. They are dependent on warmth, ceasing when the slide is removed from the thermostat or allowed to cool, and beginning again when it is warmed. I have seen a few move in midsummer at a temperature of 29.5° C. In the only experiment made to test the vitality of the sporozoites after the death of the host they retained their power to move for at least 4 days, the mouse tissues being kept in the refrigerator in the meantime and examined from day to day.[12] These observations lead to

[12] In some notes made in 1890 when this parasite came under my observation in a single case (Washington, D. C.) the same peculiar movements are recorded. The

the inference that the sporozoites, owing to their perishable nature, must enter another host, presumably warm-blooded. The movements simulate a boring or screw-like action, which may come into play when they penetrate the mucosa.

When muscular tissue containing the matured sporozoites was fed to mice, no evidence of any invasion of the muscle fibres was obtained until approximately the 45th day, when the smallest parasites were first detected. The youngest parasite which I have recognized in fresh tissue was a fusiform body .152 mm. long and .02 mm. broad (Plate IV, Fig. 8). This stage consists of a delicate, structureless membrane whose contents, in the fresh condition, are hyaline and practically invisible. A moderate number of minute, scattering, refringent granules appear in its substance, which are of substantial aid in finding it. In somewhat later stages when the parasite has grown much longer, its substance is found divided into a number of broadly fusiform bodies whose long axes are nearly parallel to that of the mother tube (Plate II, Fig. 4). In this stage the parasite readily slips out of the muscular fibre in which it is lodged, when the fresh tissue is teased. It suggests a tube densely packed with small fish. These primary divisions of the parasite are .012 mm. long and .004 mm. broad in the middle. Each is provided with a spherical highly refringent granule .001 mm. in diameter blackening slowly in osmic acid. It is contained in a minute vesicle. Beyond this the fusiform bodies reveal no structural details. Individuals are now and then found in which the division, completed in some parts, lags behind in others. The bluntly rounded ends of the parasite are usually behind the rest of the body in this respect.

This primary stage of the fusiform bodies is followed by another, seen first in the central portion of the tube. Here the parasite becomes broader and more opaque owing to the presence of closely packed crescentic or kidney-shaped bodies (Plate IV, Fig. 11). Just what change takes place in the fusiform bodies which leads to the crescents I am unable to state. Certain appearances suggested a

sporozoites of the Sarcosporidium of sheep are described by L. Pfeiffer (*Die Protozoen als Krankheitserreger*, p. 123. Jena, 1891) as becoming amœboid when warmed in human saliva.

longitudinal cleavage of the former. One parasite in this transitional stage I was fortunate enough to obtain, by teasing, completely freed from its encasing fibre. It was about 4 mm. long and .026 mm. broad.

In about 70 days after feeding the parasites enter the stage of spore and sporozoite formation. The substance of the parasite is now found to be made up of relatively large roundish or polyhedral masses of a finely granular appearance which are in close apposition with one another and .014 mm. to .016 mm. in diameter (Plate IV, Fig. 12). These sporoblasts soon break up into the final sporozoites, the exact number of which I have not been able to determine. Probably eight are formed from each sporoblast. The continuous growth and breaking up of the sporoblasts causes enough internal pressure to force the sporocysts to assume a flattened outline within the parent tube, with their long diameter at right angles to that of the latter. The whole suggests the appearance presented by dried figs in their original package. The stage of the unsegmented sporoblast I have rarely seen, and I think it is of short duration, the sporocyst following closely upon this stage. Rarely sporoblasts and sporocysts are found in different sections of the same individual at the same time. As stated above, the ripe sporozoites readily escape from the parasitic tube when fresh tissue is teased. A similar escape is not observed, however, in any of the preceding stages. Neither the fusiform nor the succeeding crescentic bodies leave the parent tube when the latter is torn unless decomposition has set in or a one per cent solution of acetic acid be added.

The account given above implies that the partitions within the Sarcosporidium are not ingrowths from the external wall as is frequently claimed, but that they are simply the walls of the sporocysts in close apposition with one another. I have seen nothing in my observations that would lead me to accept any other view with reference to the species under consideration.

Sarcocystis muris thus ripens within the muscular tissue in 2½ to 3 months after the date of feeding. Ingestion of infected muscle at this final stage by another mouse is followed by a similar infection of the muscular system.

It was not my purpose at this time to enter into any study of the morphological details of the various stages in the intra-muscular life of this Sporozoon. It seemed, however, desirable to confirm the observations made with fresh tissues upon such as were fixed and hardened and stained according to current methods. In doing this the following plan was adopted:

Muscular tissue from chloroformed mice was fixed for 24 hours in Zenker's fluid and then, after thorough washing, was hardened in ascending strengths of alcohol. The tissues were embedded in paraffin after passing through cedar oil and cut in ribbons. Various stains were employed, such as the various hæmatoxylin preparations with or without eosin and picro-acid-fuchsin; also eosin and Unna's polychrome methylene blue, and Heidenhain's iron hæmatoxylin. The best stain I found to be hæmatate of ammonia, which I had prepared myself and which stained rather slowly and chiefly nuclear matter.

In the earliest intra-muscular stages of the parasite seen, a multiple division of the nucleus was already under way (Plate I, Fig. 2, and Plate II, Fig. 3). The entire substance was mapped out into a large number of areas having certain definite characters. Each area consisted of a rather dense nuclear body, .002 mm. in diameter, and with faintly lobulated periphery occupying a clear space 2 to 3 times its diameter. Within this space and a somewhat variable distance from the nucleus was another body, perfectly spherical, about .0005 mm. in diameter and staining compactly with chromatin dyes. The significance of this minute satellite accompanying each nucleus must be left to future cytological studies.[13] All that I can state now is its unvarying presence in this early stage. It has not been described by Bertram,[14] who has studied the early stages of other species of Sarcosporidia.

A division into separate individuals or cells was not noticed in the earliest stages. Somewhat later fusiform bodies appear in outline, each of which contains the nucleus and the micro-nucleus or karyosome above mentioned. The latter, however, soon disappears.

Beyond this the study of stained sections has not thus far contributed anything material to the facts brought out by the study of fresh tissue. No clue concerning the suspected division of the fusiform bodies before they enlarge into the sporoblasts was obtained. Nor did the examination of sections from a number of cases reveal the processes in the

[13] For similar bodies in the development of trypanosomes of gray rats see Rabinowitsch and Kempner, *Zeitschr. f. Hygiene*, 1899, xxx, p. 251.

[14] *Zoolog. Jahrb., Abtheilung f. Anat. u. Ont.*, v.

sporoblasts which end in the breaking up of these into sporozoites. Evidently these changes go on very rapidly and are encountered only through lucky accidents rather than carefully planned and executed experiments.

This fragmentary statement of what seem to be the stages leading to the formation of the sporozoites has been introduced simply as a stimulus to a more thorough study of this parasite, which feeding experiments enable us now to obtain in any desired amount. The statements of other observers point to a similar complex development of other members of this genus. Thus Bertram,[15] in a study of the Sarcosporidia of sheep speaks of the earliest divisions or cells as mother-sporoblasts, implying thereby a further division before the stage of sporoblast is reached. L. Pfeiffer[16] thinks that there may be crescentic bodies of the second, third, etc., generation.

EXPERIMENTAL DATA AND RESULTS.

Since the experiments whose results I have briefly given are the first in which feeding has been successful, it is necessary to go somewhat into detail concerning the experiments themselves in order to point out the difficulties and limitations inherent in work of this kind to which bacteriological methods are inapplicable. The details which require special attention are: (1) the source of the animals used; (2) the food; (3) the association of the animals with one another in confinement; (4) the ecto-parasites of mice; and (5) the method of feeding the infected material.

1. The common gray house mouse was used almost exclusively. A few white mice and crosses were included and the results indicated equal capacity for infection. Since it is impossible to tell, without removing bits of muscular tissue by a surgical operation, whether any mouse is infected spontaneously, even a severe infection being compatible for many months with a sleek appearance and the usual vivacity, control observations were made upon mice during the whole period of the investigation. The surgical operation referred to was

[15] Loc. cit.

[16] *Die Protozoen als Krankheitserreger*, p. 119. Jena, 1891.

considered inapplicable in the case of such small animals, not to mention the chances for missing slight infections. The chief source of the mice was a room where the small laboratory animals were kept. Mice caught in this room as well as elsewhere were examined microscopically. Portions of muscular tissue were teased fresh in normal salt solution and carefully scrutinized with the 16 mm. and 4 mm. objectives for those earlier stages which are not visible to the naked eye. 155 control mice, of which 120 were from the animal room above referred to, were examined in this way. Of the 35 from outside sources, one was found infected. Of the 120 from the animal room examined over a period of 3 years, 8, or about 6⅔%, were found infected. This rather high rate of infection is probably due to the fact that before attention had been directed, in the spring of 1898, to the infected cage a mouse may have occasionally escaped from it and carried the infection into the hiding places. A tabulation of all the facts bearing upon these control mice showed that there was, during the winter months of both 1900 and 1901, a slight wave of infection, which, judging from the age of the Sarcosporidia, started near the beginning of December. It was almost wholly confined to the large adults, male and female, and was most probably due to some old mouse killed and partly consumed by others.

2. The association of mice in confinement may lead to general infection if a spontaneously diseased mouse should die in the cage. In order to eliminate this source of error the mice were either transferred directly to glass jars, one or two in a jar, or else when they were stored in cages in larger numbers, any that died or were removed for other purposes were carefully examined.

3. The food of the mice was at first bread and oats, later oats almost exclusively. The possibility that the oats might be contaminated led to steaming them before use. The general outcome of the experiments does not favor the hypothesis that infection may occur in this way. The bedding for the jars was carefully selected from hay and straw, and in the later experiments was sterilized dry as a final precaution.

4. The negative outcome of the feeding experiments of former

observers taken together with the somewhat unexpected results of investigations upon other Protozoa which demonstrated that arachnids are the transmitters of bovine malaria (Texas fever), mosquitoes of human malaria, that flagellates in the blood of rats are transmitted by fleas, in the blood of larger animals by a fly (*Glossina morsitans*), made it necessary to examine any possible relationship between sarcosporidiosis in mice and certain ecto-parasites which infest them. There is, however, no close analogy between the transmission of microorganisms circulating freely in the peripheral capillaries and such parasites as are situated more deeply and securely in the muscle fibres. The ecto-parasites of the mice which came under my observation were two species of mites, *Myobia musculus* and *Myocoptes musculinus*. They were either found on different animals at different times or else associated together on the same individuals. In order to bring them into view, the skin of the chloroformed mouse was left from a few to 24 hours under a bell-glass. Any mites would then appear on the hairs, usually near the tips. *Myocoptes* was first encountered as a delicate woolly scab around the base of the ears. In this colonies of eggs and immature young were found. More rarely colonies of young were found in the subcutis as round, flat masses not more than 1 mm. in diameter and resembling a little bit of circumscribed adipose tissue. Adult *Myocoptes* were occasionally found in large numbers on unthrifty caged mice. As a rule mice confined together in numbers up to 15 or 20 were infested.

The possible relation of these mites to the sarcosporidia was carefully taken into consideration by noting their presence or absence on the animals examined. As they are very small and cannot be made out distinctly without a hand-lens, they may be overlooked when very few are present.[17] They did not seem to bear any etiological relation to the muscle parasite. They were frequently noted as absent in positive cases and very numerous in negative cases. Long cohabitation with infected mice in the presence of these mites did not increase the opportunity for infection, as will be pointed out farther on.

[17] *Myobia* is about .5 mm. long and .2 mm. broad. *Myocoptes* is about .3 mm. long and .13 mm. broad. These dimensions apply only to adults.

5. As stated above, the mice used in the experiments were either kept before the feeding in lots of 10 to 15 in large cages made of wood and fine-meshed wire, or else they were placed directly into glass jars. Ordinary battery jars, 6 by 8 inches, were covered with a galvanized-iron wire top with meshes too small to admit house flies. From this top a small glass dish to hold water was suspended with copper wire. The drinking water was renewed by removing the wire top and slipping a glass plate in its place temporarily. The drinking dish left attached to the wire top was rinsed and filled and the top replaced. This arrangement kept the bedding dry and the jars were changed but once in three weeks. The grain was poured into the jar and the hulls slowly accumulating were removed when the jar was changed. In such jars two, very rarely three, were kept.

In experiments from No. 8 to 19 of the table, the infection of the mice was effected in the following manner: Food was usually withheld for the day, and towards evening the muscular tissue of the infected mouse, freed completely of skin and entrails, was cut up into fine bits in normal salt solution. This mass was mixed with bread crumbs in a small glass dish and moistened if necessary with more salt solution. Each jar, containing one or two mice, received a dish. The amount eaten was noted next morning. In the earlier experiments the muscular tissue or a piece of the carcass was placed in the jar without any preparation, but the mice often refused to touch it. The food substances mixed with the infected flesh must be properly chosen. I have found bread crumbs softened in normal salt solution a favorite dish. In the summer of 1900 I used cornmeal, but the mice threw it out of the dishes, and I attribute the failure of certain experiments to the injudicious selection of the food. The mice to be examined were usually chloroformed, more rarely killed by a blow while under chloroform. The latter did not affect the vitality of the Sarcosporidia or of the mites.

When the preliminary experiments had made it evident that the Sarcosporidia enter the muscles by way of the digestive tract, it became necessary to determine the time after feeding when the parasites begin to appear in the muscle-fibres or can be recognized therein, and the time required for the ripening of the sporozoites. In order to eliminate errors of interpretation it was desirable to examine the animals during the earlier, most characteristic stage of the muscle parasite, because the later ripe stage remains unchanged indefinitely

and gives no clear testimony concerning the probable date of infection. To determine the time of the earliest appearance of the parasite in the muscle fibre, infected mice were killed at different periods after the feeding and the quite uniform answer given by all experiments was that the earliest stages were detected between the 40th and the 50th day after feeding.

The accompanying table has been condensed from one upon which all the details of the experiments to which any attention had been given were noted. Among these are the source, size and sex of each mouse, the date of capture, the mode of confinement and the presence or absence of mites. A study of these data led me to regard most of them as negligible factors, and they are therefore omitted from the published table.

In the examination of the mice, a careful record was kept of the stage of development of the muscle parasite, and upon this record is based the number of cases which are put down as the result of artificial infection and the number in which the infection had presumably occurred in the natural way.

Before discussing the results of the experiments as a whole, a few remarks concerning some of them may not come amiss. One of the earliest (No. 2) led me to assume erroneously that the parasite appears very soon—within a week—in the muscular tissue. Six days after the single mouse had been fed it died, and in the abdominal muscles were found the earliest segmenting stages of the parasite. Later experiments made it evident that the mouse was infected when used. Somewhat later the feeding experiments made with the carcass of infected mice yielded results which seemed to point to wound infection. Those fed with bony portions were found more frequently infected. This inference was also found to be an error and was given up when the feeding of bread with the infected muscle proved so successful. Of the later experiments, No. 12 deserves notice. The 2 mice which were caught in a distant building and did not come in contact with any others were both found in the earliest stage of infection on the 51st day. Experiments No. 13 and 14 yielded very poor results, yet these were offset by the fact that there was no evidence that any mouse had been infected before use. The partial failure to infect I attribute, as already stated, to the use of cornmeal. On several occasions I have noticed that mice recently caught in distant buildings were less inclined

Number of experiment.	Number of mice used.	Source of mice.		Date of feeding.	Manner of feeding.	Mice examined						Number evidently spontaneously infected.	Number infected by feeding.	Source of infected muscle.
						Before 45 days after feeding.		Between 45 & 60 days after feeding.		Later than 60 days after feeding.				
		Animal room.	Elsewhere.			Infected.	Not inf.	Infect.	Not inf.	Infect.	Not inf.			
1	1		1	Nov. 18, 1898	Portion of body of infected mouse.	0	1							
2	2	1	1	Jan. 4, 1899	" " " "	1	1					1		
3	4	?	?	Feb. 1, "	" " " "	0	4							
4	4	?	?	Feb. 24, "	" " " "					1	3		1	
5	2	?	?	May 20, "	" " " "					2	0		2	
6	2	?	?	May 22, "	" " " "					1	1		1	
7	6	?	?	Sept. 15, "	" " " "	0	4			1	1		1	Expt. No. 6.
8a	8	animal room	—	Oct. 3, "	" " " "	0	4	2	0	2	0		4	
8b	6	" "	—	Oct. 3, "	Muscular tissue + bread + salt sol.	1	1	4	0			1	4	Expt. No. 5.
9	11	" " &	elsewhere	Dec. 9, "	" " " "	0	7	2	0	1	1	1	2	Expt. No. 8.
10	7	1 (?)	6	Jan. 15, 1900	" " + corn meal + "	0	1	2	1	2	1	1	3	Infected cage.
11	4	3	1	Feb. 22, "	" " " "	1	0	3	0			1	3	" "
12	2		2	Mch. 28, "	" " + bread + "			2	0				2	Expt. No. 10.
13	12	9	3	May 9, "	" " + corn meal + "			4	2	2	4		6	Infected cage.
14	18	18		June 26, "	" " " "	0	6	1	2	2	7		3	" "
15	2		2	Aug. 25, "	" " + bread + "			1	0	0	1		1	Expt. No. 13.
16	10		10	Sept. 19, "	" " " "	0	1			7	2	1	6	" " 14.
17	8	4	4	Nov. 25, "	" " " "	0	1			5	2		5	Infected cage.
18	17	11	6	Dec. 18, "	" " " "	0	9			6	2		6	Expt. No. 16.
19	18		8	Mch. 23, 1901	" " " "			6	2				6	" " 17.
					Totals.....	3	40	27	7	32	25	6	56	

to eat the infected food than those caught in the animal room or confined for some time in cages or jars, where food was always plentiful. Possibly the changed environment leads to a more voracious appetite, which may influence the results of experiments. In not a few instances only one of two mice fed together in the same jar was found infected.

Before leaving the subject of minor details, I shall give an account of Experiments No. 18 and 19, which may be taken as a type of the later ones. In No. 18, 18 mice were used, of which one was found dead in the course of the experiment, but too late to be examined, leaving 17. 11 of these were from 3 cages stocked during the summer of 1900. Control examinations of all that died in the cages were made. Two from a distant house were placed together in a jar. Four were white mice raised in another house and also kept by themselves. On the day of feeding the 11 gray mice had been confined for 3 to 4 months and were not very thrifty. Of these, 9 were chloroformed from 2 to 41 days after feeding, but no infection was detected. The remaining 2 were examined on the 60th and 62d days respectively, and the infection was found in the early stages. The 2 gray mice from a distant house confined only 2 days before feeding refused the infected food. Both were found free from infection on the 94th day. The 4 white mice were examined 67, 69 and 85 days after feeding and were found in stages of infection corresponding to the assumed cycle of development of the parasite. Both negative and positive cases were infested with mites.

In No. 19, all the mice were from a distant house and kept separate from those caught in the animal room. There were 4 jars, containing 2 apiece. Between the 50th and 60th days all were chloroformed. 6 out of 8 were in the earliest stages of sarcosporidiosis. In two jars both mice were affected. In the remaining two, only one each. A fifth pair of mice from the same source, and kept in the same way as controls, were killed at the same time. Both were free from infection.

Turning to the results of these experiments, we find that of 43 mice killed before the 45th day, 3 were infected. On account of the advanced stage of the parasites, these are classed as infected before use. Of the 34 killed between the 45th and the 60th day, 27 were infected. Of these, one is classed with the spontaneous infections. Of the 57 killed after 60 days, 32 were infected. Of these, 2 are rejected as previously infected. Taking all together, we have of 91 examined after 45 days, 59 infected, 32 not. Rejecting 3 of these, we have an infection of 63.6% after 45 days. If we compare the

spontaneous infections discovered in the experimental mice with those of the mice examined as controls, we find a close agreement. Eliminating from both series all mice caught outside of the animal room, we find the control series of 120 mice from the animal room yielding a spontaneous infection of $6\frac{2}{3}\%$, the experimental series, of $6\frac{2}{3}\%$ also, if we include in this series all mice whose source is indicated as doubtful in the table, which would make 90 in all. It is highly probable that all mice marked doubtful came from the animal room.

It is of interest to compare with these statistics those of the permanently infected cage. When the disease was first discovered it was thought that simple cohabitation might induce it, and hence fresh mice were introduced from time to time. To make sure of the persistence of the infection, the bodies of infected mice were placed in the cage temporarily from time to time. In Feb., 1900, a jar containing bits of infected muscular tissue mixed with bread crumbs was put into the cage. 76 days later, 6 out of the remaining 10 mice were found infected. 4 were in the earlier stages, suggesting the last feeding as the cause; 2 were in advanced stages. Whether they were also infected with younger stages was not noted. Of the 39 mice taken from this cage of which I have any records, 19 were infected, 20 free, yet all had been in the cage from 6 to 12 months and continuously exposed to mites and fecal discharges, and all had had an opportunity to infect themselves by feeding. Under these conditions about 50% became diseased, whereas in the feeding experiments the net positive result is 63.6%

The life history of *Sarcocystis muris* as interpreted by the results of the foregoing experiments consists in the invasion of the muscular system of the mouse by sporozoites taken in with the food. The sporozoites being contained in cysts cannot escape, and the infection can take place only when muscular tissue is eaten. The long period between infection and the growth of the parasites in the muscle fibres might be interpreted in two ways:

1. The parasite requires a long time to store up enough energy to undergo the rapid growth and multiple division of the nucleus terminating in the formation of spores and sporozoites. Similarly long

periods are required by the various Cysticerci of the common tapeworms of man to reach the—for them—mature stage.

2. The sporozoites after ingestion develop into sexually mature organisms in some part of the body in a manner analogous to the genus *Coccidium*. After fertilization the female organism (macrogamete) migrates into the muscle fibres and there passes through the process of sporogony.

This second hypothesis seemed the more attractive one at the outset and much time was devoted to tracing the hypothetical sexual elements in various organs of the body. Especially the intestinal tract was scrutinized carefully in animals killed at stated intervals after infection. The intestinal contents, the epithelium and the submucosa were searched in fresh preparations, in some cases in sections, for any forms which might be taken for the parasites sought for. The fate of the sporozoites soon after feeding was investigated, but no traces of them found. The spleen, kidneys and the bone-marrow, as well as the blood, received attention but nothing definite was discovered.[18]

Another view suggested itself as an outgrowth of the second. It was assumed that the sporozoites became sexually mature in the intestines, were discharged and then ingested either by the same host or other mice. This hypothesis was discredited by the impossibility of producing the disease by simple cohabitation in infected cages. Yet the occasional discovery of minute coccidia-like bodies in the intestinal contents led to a more thorough search without, however, leading to any result. The following experiment was also made. Two white mice from Expt. 18, kept together in the same jar, were transferred to fresh jars on the 2d, 3d, 4th, 6th, 8th, 9th and 11th day after feeding, to remove any hypothetical, sexually mature elements discharged with the feces. The mice were nevertheless found severely infected in due time.[19]

My observations have thus not yet bridged the gap up to the 6th week. Careful examinations of the fresh muscular tissue of mice

[18] In the spleen I encountered quite regularly the large giant cells of the bone marrow.

[19] In the digestive tract of many mice kept confined for some months and not very thrifty, two flagellates, *Lamblia intestinalis* and a trichomonas-like form were frequently encountered in the small intestine together with an amœba in the cæcum. These protozoa it was believed bear no genetic relation to *Sarcocystis muris*.

killed earlier than this have been made in large numbers, but they are not sufficient in themselves to warrant the assumption that the immigrated sporozoite is not present much earlier than this. The examination of stained sections in considerable numbers will be necessary. It may be found that the parasite reaches the muscle fibre soon after ingestion, where it remains undetected until the multiple division of the nucleus begins and the organism by its rapid growth and increased affinity for chromatin dyes becomes recognizable. The parasite reproduced in Plate I, Fig. 2, which was found 51 days after feeding, measured only .05 mm. in length and .016 mm. at its greatest width. These dimensions are four times those of the sporozoite—a very slight increase in this long period of time.

There are several aspects of this whole subject which have suggested themselves in the course of the investigation and which I shall touch upon very briefly.

The infected tissue used for feeding came, in about one-half of the experiments, from mice taken from the infected cage. In the other half, mice from one of the preceding experiments were used as indicated in the table. In the later experiments it became evident that the Sarcosporidia developed somewhat more slowly than in the earlier, and that the fully matured muscle parasites were smaller than in the earlier, and in the spontaneous infections, due not to any shrinkage in size of the sporozoites but to a smaller number. This apparent degeneration may be due to the feeding of tissue from artificial infections—a kind of artificial cultivation of the parasite under slightly abnormal conditions, such as monotonous diet and confinement of the host. It may also be due to the need of passing temporarily to some other host, or perhaps to other still unknown causes.

Can mice be infected twice or oftener, or does the first feeding establish immunity? This question was approached in one experiment. Two mice in Expt. 17, fed Nov. 25, 1900, were fed again after 55 days on Jan. 19, 1901. They were killed March 22, about 4 months after the first, 2 months after the second feeding. There was an abundant invasion due to the first feeding, but none traceable to the second feeding. Simultaneous feeding of other mice on Jan. 19 was successful.

Another question which has an important bearing on the outcome of feeding experiments is that of an initial immunity which may lead to a destruction of the sporozoites before they reach the protecting envelope of the muscular fibre. That such immunity exists is suggested but not demonstrated by the general outcome of the investigation. I have already referred to the disinclination of recently caught mice to eat muscular tissue mixed with bread, but this only partly explains the results.

May sporozoites infect when injected into the subcutis or the abdominal cavity? With the earlier feeding experiments, 5 separate tests were made to solve this problem. The results, though leaning decidedly towards the negative, were not quite satisfactory and will have to be repeated on a larger scale.

I have left the chapter on the pathology of sarcosporidiosis in the mouse, as well as the toxicity of the sporozoites, as brought out by L. Pfeiffer[20] for the parasite in sheep, and subsequently by Laveran and Mesnil[21] for the same species, for special consideration. In general the tissue reaction appears to be very slight during the developmental period of the parasite. Multiplication of muscle nuclei, scattering, small foci of leucocyte infiltration associated with slight cell proliferation of the perimysium internum and the sheath of the small vessels are usually present, but they apparently stand in no direct relation to the invasion, for the affected fibre and its immediate environment are in nearly every case normal. To interpret the slight changes present, the condition of the muscular tissue preceding visible invasion will need special attention. When the parasites are very large and numerous, as in Plate I, Fig. 1, disturbances in the movements of the animal should occur, and as a matter of fact such mice are frequently found slow in movement and ill. The sporozoites in the old cysts may shrivel and disappear and leave the chambered cysts empty as in Fig. 1. In one case I found them filled with polymorphonuclear leucocytes.

The life histories of all Sarcosporidia are not necessarily explained by the results obtained with *Sarcocystis muris*. It would be difficult, for instance, to account for the Sarcosporidia of cattle in the way those of mice can now be accounted for, since cattle are not carnivorous. Their muscle parasite is either an aberrant form from some invertebrate taken in with their food or else there is an intestinal stage as

[20] Op. cit., p. 123.

[21] *Comp. rend. Soc. de biol.*, 1899, p. 311.

well, which readily permits a discharge of spores outwards. It is obvious that other views or modifications of the views presented might be brought forward, but I desist from any further discussion not based on actual studies.[22]

The experiments described in the foregoing pages warrant the conclusion that the feeding of *Sarcocystis muris* containing ripe, mobile sporozoites to gray and white mice is followed by an invasion of the muscle fibres by the parasites, which become readily recognizable after the 45th day. At this time the parasite is, as a rule, many times larger than the sporozoite which it presumably represents. Within 2½ to 3 months the parasite has reached the final stage, in which it consists of a chambered cyst filled with sporozoites, mobile at the temperature of the body and capable of infecting other mice.

DESCRIPTION OF PLATES I-IV.

PLATE I.

The photomicrographs were made by Mr. L. S. Brown in the clinico-pathological laboratory of the Massachusetts General Hospital through the courtesy of Dr. James H. Wright, Director.

Fig. 1. Photograph. Extensive invasion of the muscular system of a gray mouse. Parasites matured, many times broader than the muscle fibres in which they originally lodged; cut obliquely. In the centre of the figure are two parasites in which only remnants of the sporozoites are present. The chambered interior is well defined. ×50.

Fig. 2. Photograph. A very early stage of *Sarcocystis muris* in the muscle fibre 51 days after feeding (Expt. No. 12). The granular appearance of the parasite is due to the presence of large numbers of nuclei. Each dark granule represents a nucleus. ×350.

PLATE II.

Fig. 3. Photograph. An early stage of *Sarcocystis muris* undergoing multiple division of the nucleus. In the two lowest nuclear areas the micronuclei are visible. Owing to the obliquity of the section only a portion of the parasite is included. From Expt. No. 9, 46 days after feeding. ×750.

Fig. 4. Photograph. An early stage from a teased preparation of fresh muscular tissue in normal salt solution. The parasite slipped out of its muscle fibre during the teasing, a frequent occurrence in this stage. The earliest division into fusiform bodies is completed. The parasitic tube is packed with fish-like bodies in some of which the refringent spherule is recognizable. ×650.

PLATE III.

Fig. 5. Photograph. Ripe sporozoites from a torn parasite. Dried lightly on a cover-glass, fixed in alcohol and ether, and stained in hæmalum. ×400.

Fig. 6. Photograph. An early stage showing the fusiform and crescentic bodies (sporoblasts or mother-sporoblasts). Hæmalum. ×625.

[22] See a paper by the writer "On a sporozoon in the intestinal villi of cattle" in Bulletin No. 3 of the *Bureau of Animal Industry*, U. S. Dept. Agriculture, p. 73. Washington, 1893.

PLATE IV.

Fig. 7. *Sarcocystis muris*, ripe stage. Natural size. From a specimen in Kaiserling's fluid.

Fig. 8. Very young stage as it appears in fresh muscle tissue in normal salt solution. The double-contoured cuticle encloses a pale, apparently structureless body substance in which refringent particles are sparingly present. × 200.

Fig. 9. A somewhat later stage under the same conditions. The refringent granules, of several sizes, are quite abundant. × 230.

Fig. 10. Stage of multiple nuclear division, corresponding to Fig. 3. To show the nuclear area, which includes the nucleus and micronucleus. From the abdominal muscles of a mouse in Expt. No. 9, 46 days after feeding. Hæmalum. For greater clearness of detail, only four are shown. Compare Fig. 3. × 1200.

Fig. 11. The stage immediately following the one characterized by the fusiform bodies of Fig. 4. The crescentic, or kidney-shaped bodies are the future sporoblasts. Each contains one or several refringent granules. Fresh preparation. × 400. (Figs. 8, 9 and 11 are from infections in Expt. 19.)

Fig. 12. The stage of sporoblasts. The latter merely outlined with the camera lucida. The outlines represent the future partitions or sporocysts. The striated margins belong to the remnants of the muscle fibres in which the parasites are lodged. From Expt. 16, 4 months after infection. Development somewhat delayed. × 280.

FIG. 1.

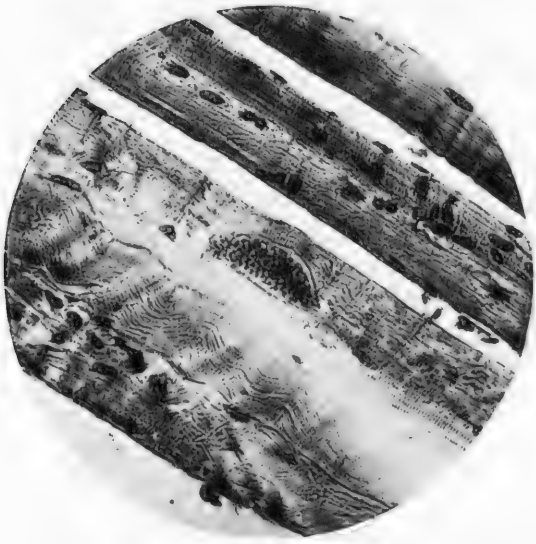

FIG. 2.

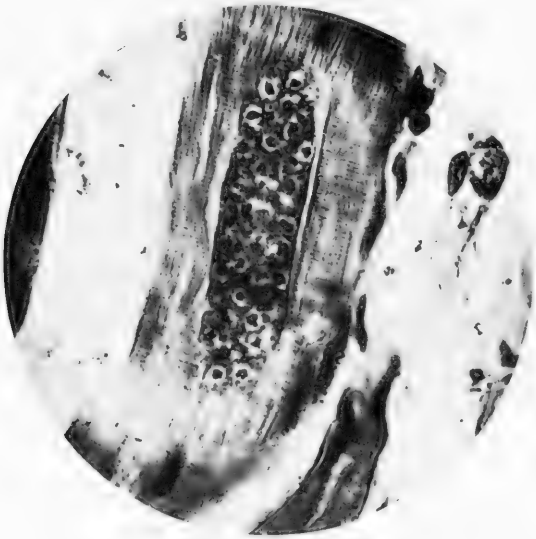

FIG. 3.

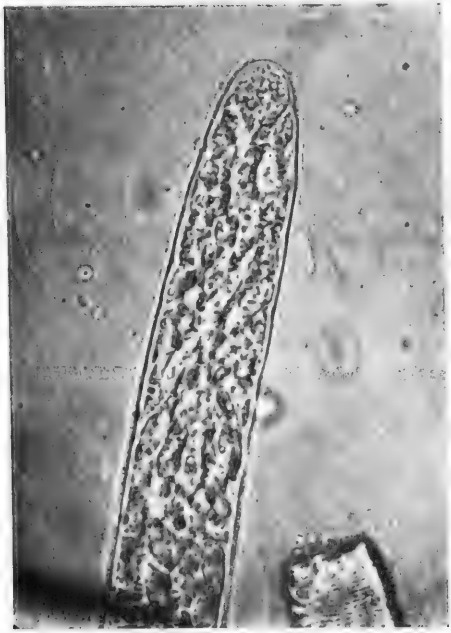

FIG. 4.

FIG. 5.

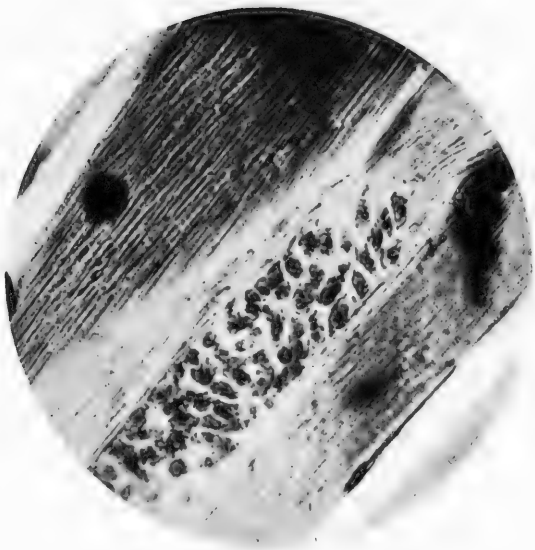

FIG. 6.

FIG. 7.

FIG. 8.

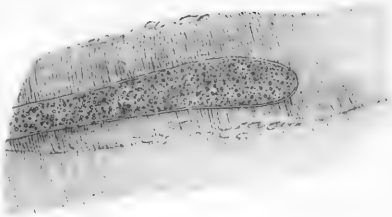

FIG. 9.

FIG. 10.

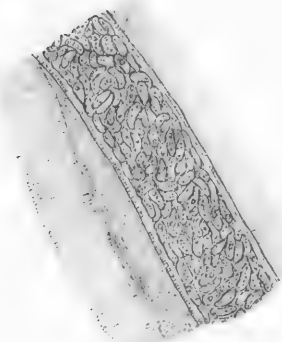

FIG. 11.

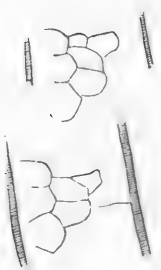

FIG. 12.

A STUDY OF CHRONIC HYPERPLASTIC TUBERCULOSIS OF THE INTESTINE, WITH REPORT OF A CASE.*

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INTRODUCTION.

During the last ten or twelve years a few writers, particularly French and German observers, have from time to time called attention to the existence of a form of tuberculosis affecting various segments of the intestinal tube and characterized by a variable but usually a considerable degree of thickening of the wall of the intestine. So definite and constant is this distinguishing characteristic that the type has been habitually referred to by French writers as *tuberculose intestinale à forme hypertrophique*. This term, however, appears to me misleading; the fundamental lesion is one of hyperplasia, hence the designation of Coquet[1]—hyperplastic tuberculosis—is certainly more correct in a pathological sense.

* An abstract of this paper was read before the New York Pathological Society, March 29, 1900.

[1] De la variété chirurgicale des tumeurs cæcales tuberculeuses. Thèse de Paris, 1894.

Ordinarily localized in the ileocæcal region, but likewise affecting other regions less frequently, the process effects a disease of long duration, the most conspicuous feature being the more or less extensive formation of fibrous and tuberculous granulation tissue in the implicated parts. This is often of such a character that the inflammatory hyperplasia or "pseudo-neoplasm" (Benoit) may easily be mistaken clinically for tumor-formation of the locality resembling carcinoma.

A condition more or less similar has been described in the larynx; its clinical presentation is also that of cancer of the part.[2] In serous membranes hyperplastic tuberculosis is also observed; the peritoneum, pleura, and especially the joints are affected in this way. Recent studies further show a more or less parallel process in a group of cases diagnosticated as Hodgkin's disease, but which fuller investigations have shown to be incited by Bacillus tuberculosis. For a knowledge of this form of tuberculous adenitis we are especially indebted to the contributions of Weishaupt,[3] Brentano and Tangl,[4] Duclion,[5] and Courmont, Tixier and Bonnet.[6] In processes of this kind the tubercle bacillus and its products induce fibrous hyperplasia rather than caseation and necrosis.

HISTORICAL.

Since the first detailed study of this peculiar type of intestinal tuberculosis by Hartmann and Pilliet[7] in 1891, it has been the source

[2] J. A. Doléris, Laryngite hypertrophique; tuberculose et sclérose partielle du poumon. *Bull. de la Soc. anat. de Paris*, 1876, li, p. 128.

Lermoyez, Végétation tuberculeuse énorme, formant polype mobile, implantée au bord de la corde vocale droite et à son insertion antérieure, etc. *Ann. d. mal. de l'oreille, du larynx*, etc., Paris, 1884, x, p. 183.

J. N. Mackenzie, Tuberkulöse Tumoren des Kehlkopfes und der Luftröhre. *Wien. med. Presse*, 1885, xxvi, p. 473.

[3] Ueber das Verhältniss von Pseudoleukämie und Tuberkulose. *Arb. a. d. path.-anat. Inst. zu Tübingen*, 1891-2, i, p. 194.

[4] Beiträge zur Aetiologie der Pseudoleukämie. *Deutsch. med. Woch.*, 1896, xvii, p. 588.

[5] Sur l'étude clinique et expérimentale de la lympho-sarcomatose et de la tuberculose hypertrophiante méconnue des ganglions lymphatiques. Thèse de Bordeaux, 1896.

[6] De la lymphadénie tuberculeuse ganglionnaire et viscérale. *Journ. de physiol. et de pathol. gén.*, 1899, i, p. 826.

[7] Notes sur une variété de typhlite tuberculeuse simulant les cancers de la région. *Bull. de la Soc. anat. de Paris*, 1891, p. 471.

of considerable interest and some discussion. To the best of my knowledge the earliest serious investigation of this anatomical type begins with these writers, the one investigating the pathological side, the other the clinical features of the disease. True, a few isolated examples of its recognition may be found in the literature prior to that date.

Thus von Hacker [8] in 1888, Suchier [9] in 1889, and Gussenbauer [10] the following year had each reported cases of this nature. As early as in 1886 Czerny [11] is said to have operated on two cases for ileocæcal disease which proved to be tuberculous; the publication of the reports, however, did not take place until 1890. Billroth,[12] in 1891, at a meeting of one of the Vienna societies, showed an amputated cæcum which had been taken out supposedly for carcinoma; the tumor was proved to be tuberculous.

But notwithstanding these earlier reports, insistence upon certain distinguishing peculiarities is the credit of the French investigators. The publication of Hartmann and Pilliet in 1891 inspired considerable interest in the subject; so that in the following two years papers on the same theme appeared by Obalinski,[13] Koenig,[14] Le Bayon,[15] Sachs,[16] Pollak,[17] Zahlmann,[18] Vohty,[19] Reclus,[20] and several others. By 1893,

[8] Ueber die Bedeutung der Anastomosenbildung am Darm für die operative Behandlung der Verengerungen desselben. *Wien. klin. Woch.*, 1888, i, pp. 359; 389.

[9] Beitrag zur operativen Behandlung der Coecumtumoren. *Berl. klin. Woch.*, 1889, p. 617.

[10] Quoted by Fink: Ueber zwei Fälle von Resection des Coecums wegen Tuberculose. *Prag. med. Woch.*, 1890, xv, p. 101.

[11] Ueber die chirurgische Behandlung intraperitonealer Tuberkulose. *Beitr. z. klin. Chir.*, 1890, xi, p. 73.

[12] *Wien. med. Presse*, 1891, p. 193.

[13] Ueber Laparotomie bei innerem Darmverschluss auf Grund eigener 110 Fälle. *Arch. f. klin. Chir.*, 1894, xlviii, p. 1.

[14] Die stricturirende Tuberculose des Darms und ihre Behandlung. *Deutsche Zeitsch. f. Chir.*, 1892, xxxiv, p. 65.

[15] De la typhlite tuberculeuse chronique. Thèse de Paris, 1892.

[16] Ein Beitrag zur Extirpation des Blinddarms wegen Tuberculose. *Arch. f. klin. Chir.*, 1892, xliii, p. 429.

[17] Ein Fall von Darmtuberculose mit schwarzem Harn. *Berl. klin. Woch.*, 1892, p. 688.

[18] Tuberkulos Tarmstricktur; resectio intestini cœci. *Hospitalstidende*, 1892, 3. R., x, p. 901.

[19] Tuberkulos Tarmstriktur; resectio intestini ilei. *Hospitalstidende*, 1892, No. 44.

[20] Typhlite et appendicite tuberculeuses. *Bull. méd.*, 1893, vii, p. 587.

Benoit[21] had been able to collect twenty-one such examples. Since Benoit's monograph a considerable number of new and interesting facts have been contributed by Luzzato,[22] Delbet and Mouchet,[23] Cornil and Marie,[24] Tissier,[25] Coquet,[26] Pasca,[27] Koerte,[28] Courteville,[29] Durante[30] Desplats,[31] Courtillier,[32] Caminiti Vinci,[33] Nové-Josserand,[34] Chavannaz and Carrière,[35] and a few other writers. In 1898 Itié[36] had gathered reports of forty-one new cases surgically treated, and Conrath,[37] in his paper published the same year, mentions a total of eighty-five. Itié's thesis is an admirable critique and presentation of the ensemble of the whole question; Conrath's paper contains the best general discussion of the subject, particularly in its surgical aspects. For the most part, all the cases reported relate to ileocæcal affections.

It is interesting to note how closely our knowledge of this form of intestinal tuberculosis is linked with the development of surgical intervention in the ileocæcal region.

The most recent contributions to the subject have been made by

[21] Tuberculose locale chronique de la région iléocœcale. Thèse de Paris, 1893.

[22] Tuberculosi della porzione ileo-cecale dell' intestino. *Riforma medica*, 1893, ix, pt. 1, p. 795.

[23] Rectite hypertrophique proliférante et sténosante. *Arch. gén. de méd.*, 1893, ii, pp. 513; 668.

[24] Observation de tuberculose du cæcum simulant un cancer de cet organe. *Congrès pour l'étude de la tuberculose* (1893), Paris, 1894, iii, p. 504.

[25] Infiltration embryonnaire de l'uterus, des ovaires et des tuniques de l'intestin. *Bull. Soc. anat. de Paris*, 1894, viii, p. 40.

[26] Op. cit.

[27] Tuberculosi del ileo-cæcum. *Gazz. med. di Roma*, 1894, xx, pp. 217; 385.

[28] Zur chirurgischen Behandlung der Geschwülste der Ileocöcalgegend. *Deutsche Zeitsch. f. Chir.*, 1894-5, xl, p. 562.

[29] Tuberculose avancée de la valvule ileo-cœcale; fistules, typhlite et appendicite tuberculeuse. *Jour. d. sci. méd. de Lille*, 1895, ii, p. 624.

[30] Resezioni intestini per tuberculosi de cieco. *Rif. med.*, 1895, iv, p. 616.

[31] Tuberculose pulmonaire localisée. Généralisation au pharynx et à tout le tube digestif pendant le cours d'une fièvre typhoide. *Jour. de sci. méd. de Lille*, 1896, i, p. 577.

[32] Tuberculose chronique de l'angle ileo-cœcal. *Bull. Soc. anat. de Paris*, 1896, x, p. 413.

[33] Resezione dell' intestino per tuberculosi, *Rif. med.*, 1896, No. 3, p. 112.

[34] Tuberculose localisée du cæcum traitée par la simple laparotomie. *Lyon méd.*, 1896, lxxxii, p. 154.

[35] Tuberculose du cœcum, etc. *Jour. de méd. de Bordeaux*, 1897, xxvii, p. 271.

[36] De la tuberculose intestinale à forme hypertrophique. Thèse de Montpellier, 1898.

[37] Ueber die lokale chronische Coecumtuberkulose und ihre chirurgische Behandlung. *Beiträge zur klin. Chir.*, 1898, xxi, p. 1.

Bezançon and Lapointe,[38] Pantaloni,[39] Monnier,[40] Claude,[41] Pozza,[42] Strehl,[43] Guinard,[44] Caussade and Charrier,[45] Hatch,[46] Obrastzoff,[47] and Tuffier.[48].

In English literature I have been able to find but three cases, that of Sainsbury[49] in 1892, that of Page[50] in 1897, and that of Lediard[51] reported the following year. Mention of four cases has been found in American literature—one by Beck[51a] in 1894 and one each by Ochsner[52] in 1895, by Senn[53] and by Cumston[54] in 1898.[55]

REPORT OF CASE.

The specimen of hyperplastic tuberculosis of the intestine which I was able to study is of the highest interest. The length of gut im-

[38] La tuberculose intestinale à forme hypertrophique. *Presse méd.*, 1898, i, p. 265.

[39] Résection de l'intestin grêle pour tuberculose intestinale chronique. *Arch. prov. de chir.*, 1898, vii, p. 327.

[40] Monnier. Contribution à l'étude de la tuberculose intestinale à forme hypertrophique. *Arch. prov. de méd.*, 1899, i, p. 92.

[41] Tuberculose hypertrophique non sténosante du gros intestin. *Comptes rend. Soc. de biol.*, 1898, p. 1110.

[42] Resezione dell' ansa ileo-cæcale et anastomosi terminale ileo-colica per invaginamento chronico causato da tuberculosi primitiva del cieco. Supplemento di *Policlinico*, 1899, p. 909.

[43] Ein Fall von fünfzehnfacher, zum Theil septischentzündlicher Darmstenose tuberculösen Ursprunges. *Deutsche Zeitschr. f. Chir.*, 1899, l, p. 411.

[44] Rétrécissements tuberculeux de l'intestin. *Bull. et mém. de la Soc. de chir.*, Paris, 1899, xxv, p. 327.

[45] Un cas de tuberculose ileocæcale à forme hypertrophique avec considérations cliniques, anatomiques et therapeutiques. *Arch. gén. de méd.*, 1899, i, p. 410.

[46] Tubercular disease of the cæcum. *Indian Med. Gaz.*, Calcutta, 1899, p. 43.

[47] Tuberculose d. Cæcum. *Arch. f. Verdauungskr.*, 1899, iv, p. 440.

[48] Rétrécissement tuberculeux à forme hypertrophique de l'intestin grêle. *Presse méd.*, 1900, p. 92.

[49] Primary tuberculous ulceration of large intestine. *Lancet*, 1892, ii, p. 367.

[50] Tuberculous ulceration of the cæcum giving rise to symptoms of disease of the appendix. *Lancet*, 1897, ii, p. 10.

[51] Excision of the cæcum for tuberculous disease. *Lancet*, 1898, ii, p. 408.

[51a] *Annals of Surgery*, 1894, xx, p. 672.

[52] Report of cases of resection of the cæcum. *Chicago Med. Record*, 1895, ix, p. 113.

[53] The surgical treatment of intestinal tuberculosis. *Journ. Amer. Med. Assoc.*, 1898, xxx, p. 1195.

[54] Tuberculosis of the cæcum. *Ann. of Gynec. and Pediat.*, 1898, xii, p. 29, (case iii.)

[55] Since the preparation of this article a valuable contribution to the pathology of chronic hyperplastic tuberculosis of the cæcum has been made by T. R. Crowder, (*Amer. Jour. Med. Sc.*, 1900, cxix, p. 668), who reports two new cases, in one of which carcinoma of the cæcum coëxisted.

plicated makes it unique in the records of this affection; and the absence of distinct stenosis and of apparent ulceration of the mucous membrane anywhere in the intestine adds further interest to the report. The atypical histological findings are so little suggestive of tuberculosis that this side of the study is particularly rich in interest. For the clinical history of the case I am indebted to Dr. J. L. Schoolcraft, of Schenectady, N. Y.

Clinical history.—Simon S., aged 49, was in active business until shortly after the onset of his trouble, when failing health necessitated inactivity. The family history shows no evidence of tuberculosis. When a child he suffered from some of the acute infectious diseases of this period, otherwise his health had always been excellent. No history of lues, typhoid, or dysentery.

In 1895, about three years before his death, he is said to have lost weight and to have become gradually weaker and weaker without apparent cause, so much so that walking became too fatiguing. On the slightest exertion a tendency to fainting had become manifest. Coexistent with this loss of strength there was noticed a change in the color of the skin; from a rather fair skin the color passed within a year to a dark brown. The distribution of the pigmentation was universal, not patchy, most accentuated on the exposed surfaces. Two months from the onset he began to suffer from cramp-like pains all over the abdomen, without definite localization; at times he thought them most intense in the right iliac region. Sometimes the attacks would last for only five minutes; more often, especially during the last year of his sickness, for half an hour or longer. For the most part the cramps came after irregular intervals of quiescence, at first, not over once a week; then later, four to eight times a day. Sometimes the attacks occurred shortly after taking food, more often without any reference thereto. Vomiting occurred from time to time, being often associated with the attacks of abdominal pain. Pressure had no effect in increasing or diminishing the severity of the pain. With time this whole chain of symptoms increased in severity. The appetite had been generally poor, the bowels irregular—alternating diarrhœa and constipation; there was a tendency to looseness, however, during the entire sickness. No mass was at any time felt by the patient in the abdomen, but a sensation of vague discomfort and heaviness was almost constantly present. Nothing abnormal had been observed about the stools; blood had never been noticed.

About a year and a half before his death he came under medical observation, when he was poorly nourished, of slim build, and complained of great weakness and loss of flesh. About thirty pounds in weight were lost in the first year of his sickness. The temperature was then normal; the skin of the face and hands, as well as of the trunk and body generally, was of a deep brownish color; in no wise was this patchy in character, nor was the pigmentation distinctly bronze-like. The mucous membranes of the lids and mouth were pale and free from pigmentation. The chest

was well developed, and the heart and lungs appeared normal. Examination of the abdomen revealed nothing, except that on deep palpation tenderness was elicited, seemingly most marked in the right iliac fossa; the spleen was not palpable, nor was the liver enlarged. Superficial glands nowhere enlarged. Urine normal. When seen for the first time, about 18 months before death, a diagnosis of Addison's disease was ventured. Arsenic, cod-liver oil, bone-marrow, and a very liberal and nourishing diet were prescribed, and he was sent to the country. For three or four months some improvement took place; he appeared to eat better, increased some in weight, and the abdominal disturbances improved considerably. Then the condition became more aggravated, with accentuation of all symptoms. During this time there was a fairly constant evening rise of 1 to 2 degrees F. About two months before death fainting fits occurred on the slightest exertion, until weakness necessitated remaining in bed for the last few weeks of life. Finally, some days before dissolution, symptoms of right-sided lobar pneumonia appeared and he died December 31, 1898.

Autopsy.—January 1, 1900, about twelve hours after death. The body had been injected with embalming fluid containing formalin, hence no cultures were made from the case. The notes from the protocol are as follows:

Anatomical diagnosis (revised).—*Hyperplastic tuberculosis of small and large intestine; lobar pneumonia of right lower lobe; œdema of lungs; tuberculosis of adrenals and of mesenteric lymph nodes; acute splenic tumor; cloudy swelling of liver; slight chronic diffuse nephritis.*

Body 160 cm. long, sparely built, moderately emaciated. Rigor mortis absent. No œdema of lower extremities. Surface of body universally of a dark brownish color, most pronounced on face and other exposed cutaneous surfaces. Nowhere is this patchy in character, nor suggestive of bronzing, but is more distinctly like the color produced by exposure to the sun. No pigmentation of buccal mucosa. Exposed mucous surfaces pale. Pupils moderately dilated and equal. Post-mortem lividity of dependent parts. Subcutaneous fat small in amount. Muscles of thorax and abdomen poorly developed and pale.

Peritoneal cavity.—Both layers smooth and normal. Foramen of Winslow patent. Congenital absence of appendix. Omentum delicate; omental glands not enlarged. Diaphragm, right side at fifth rib; left side at fifth interspace. Right lobe of liver reaches 5 cm. below costal margin; stomach not visible.

Both *pleural* cavities free from fluid, and *pericardium* smooth, its cavity containing a small quantity of clear yellow fluid.

Heart, small, distended with cruor clots; valves normal. Just above valves aorta shows diffuse areas of fatty atheroma. Both coronaries normal; myocardium firm, of a homogeneous red-brown color.

Left lung, free from adhesions, pleura smooth. Consistence firmer than normal. On section all lobes are brownish-red and exude a considerable quantity of blood-stained serum. No thickening at the apex.

Right lung.—Pleura smooth except over lower lobe, where it is covered with fibrin. Upper lobe contains a moderate amount of serum; lower lobe is solid, yellowish-gray in color, with streaks of brown or black, and finely

granular. No apical tuberculosis. Mucous membrane of bronchi congested. Blood-vessels normal. Bronchial glands slightly enlarged and pigmented, free from calcareous deposits or caseation.

Liver, free from adhesions, not enlarged, soft. Capsule smooth, section yellowish-brown or red in color, very cloudy.

Gall-bladder, normal, common duct patent.

Spleen, free from adhesions, moderately enlarged, firm (due to hardening fluid?), capsule smooth, trabeculæ not increased, Malphigian bodies swollen, pulp increased.

Kidneys.—Fatty capsule small in amount; fibrous capsule strips off easily; surface smooth. Cortex normal in amount; markings distinct; glomeruli visible; medulla and pelvis normal. *Ureters*, normal.

Pancreas, normal.

Left adrenal gland, enlarged, soft, and on section contains a pea-sized cavity, the walls of which are of a dark brown color and caseous, containing a small quantity of dark brownish-red fluid of viscid consistence.

Right adrenal gland, also enlarged, somewhat firmer than normal; on section shows a number of diffuse yellow areas suggestive of caseous material, but firmer in consequence of calcareous deposits.

Mesenteric glands enlarged and caseous; *retroperitoneal glands*, swollen to twice their usual size, but in them no distinct caseous areas can be made out.

Aorta, bladder, prostate, œsophagus, stomach, tongue, epiglottis, vocal cords and larynx, normal. Trachea moderately congested. Thyroid normal.

Intestine.—No adhesions. A noticeable thickening of the wall becomes apparent in the upper third of the ileum, the change from the normal intestine to the thickened ileum being so gradual as to be scarcely perceptible. Where the change occurs the intestinal wall feels harder, stiffer, until finally at the middle third of the ileum the gut becomes a cylindrical tube, with non-collapsible walls of firm, hard, resistant tissue. At a point corresponding to about the junction of the upper and middle thirds of the ileum the wall measures from 4 to 7 mm. in thickness. Passing downward, the thickening rapidly becomes more evident, especially in the last half metre of the small bowel, where the wall measures 1 cm. in thickness. The cæcum is thickened also and bound down laterally to the abdominal wall by old fibrous adhesions. Here the thickness of the wall measures 2.7 cm. The ileocolic valve is thickened and rather rigid, and shows no loss of substance. The ascending colon presents an appearance similar to the other thickened intestine, but measures not over 1.2 cm. near the cæcal end, and at the hepatic extremity only 0.75 cm. The transverse colon measures about the same (0.75 cm.); finally, the descending colon imperceptibly dimin-

ishes in thickness to the sigmoid flexure, where the bowel again assumes its normal proportions. The rectum is normal.

On section the thickened portions are resistant to the knife, and grey or whitish in color. The thickening is quite uniform in all parts of the circumference of the intestine, except in the cæcum, where it is most pronounced posteriorly; here the thickness being fully 1 cm. greater than anteriorly. To the naked eye the walls seem to be largely fibrous. No tubercles or caseous areas are visible. The lumen is entirely patent at all points, being quite normal in the ileum except in the lower half metre, where it appears reduced by about one-third. This narrowing of the lumen continues until the transverse colon is reached, whence the diameter gradually becomes more and more normal as the sigmoid is approached. The cæcum is free and the circumference of its lumen is 13.4 cm.; that of the ileum one-half metre above the ileocæcal valve is 7 cm.; that of the ascending colon 9 cm.

The mucous membranes of the duodenum and jejunum are bile-stained and smooth and normal in appearance. In the ileum the mucous membrane seems pale, and everywhere appears free from ulceration. The same is true of the remaining length of the canal. Now and again swollen solitary follicles may be seen in the small and large intestine; Peyer's patches appear unaffected. Beginning in the middle of the ileum the mucosa becomes thicker and thicker until the ileocæcal region is reached; in the cæcum and ascending colon it appears about the same and thereon becomes gradually normal.

The most conspicuous feature of the mucosa is the presence of numerous papillomatous masses, rather clubbed in form. They are most abundant in the lower ileum, cæcum and part of the ascending colon, where the largest attain as much as 8 mm. in length, the average size being about 4 or 5 mm. They are freely movable but rather rigid masses of tissue with narrow pedicles. They appear to be covered with normal mucous membrane. In the cæcum and ileum they are most numerous and quite closely aggregated; in the remaining portions they appear more discrete.

The peritoneal surface is everywhere smooth without evidence of old peritonitis, and shows no visible tubercles.

Microscopic Examination.—The tissues were placed in 95 per cent alcohol, Orth's fluid, and Müller's fluid. The sections were stained with hæmatoxylin and eosin, picric acid fuchsin, and by Weigert's modification of Gram's stain. For staining the tubercle bacilli several methods were employed, those of Ziehl-Neelsen and Kühne being particularly

used; the procedures of Letulle[56] and Hauser[57] were also used with good results. All of these methods were utilized, particularly with sections of the thickened intestine.

The histological examination of the various organs confirmed in the main the classification of the autopsy findings.

Sections of the *heart* showed a moderate degree of brown atrophy of the muscle; the pericardium and endocardium presented no change, and the cardiac blood-vessels were normal.

The *lungs* were moderately emphysematous, and, where not consolidated, showed considerable œdema with a fair amount of desquamation of the alveolar epithelium. Few red corpuscles and leucocytes were present. Sections from the *right lower lobe* showed complete consolidation by an exudate almost wholly of polymorphonuclear leucocytes; a small amount of fibrin, occasional desquamated cells, some granular material, and now and again a red blood-cell made up the remainder. On the mucous membrane of the bronchi was a small amount of granular material containing a few desquamated cells and leucocytes. The blood-vessels contained much blood in which a distinct and marked leucocytosis, polymorphonuclear in type, was discernible.

The *liver* showed albuminous degeneration, with here and there some fatty cells. The *spleen* contained considerable blood, apparently lying free between the pulp cells; the Malpighian bodies showed a lymphoid increase. Here and there within the cortex of the *kidney* tracts of round-cell infiltration were apparent, and the cells of the convoluted tubules were swollen and granular. The tufts showed occasional thickening of Bowman's capsule. In the medullary portion a few areas of round cell infiltration were also detected. Tubercles were absent.

Many sections of these organs—heart, spleen, lungs, liver and kidneys, but especially of the consolidated lung and the kidneys—were stained for tubercle bacilli, but none could be demonstrated. In sections of the pneumonic lung stained by Weigert's method were demonstrated a fair number of small round cocci often in chains (*Streptococcus pyogenes?*), and here and there among the cells large oval cocci arranged in pairs (*Micrococcus lanceolatus?*).

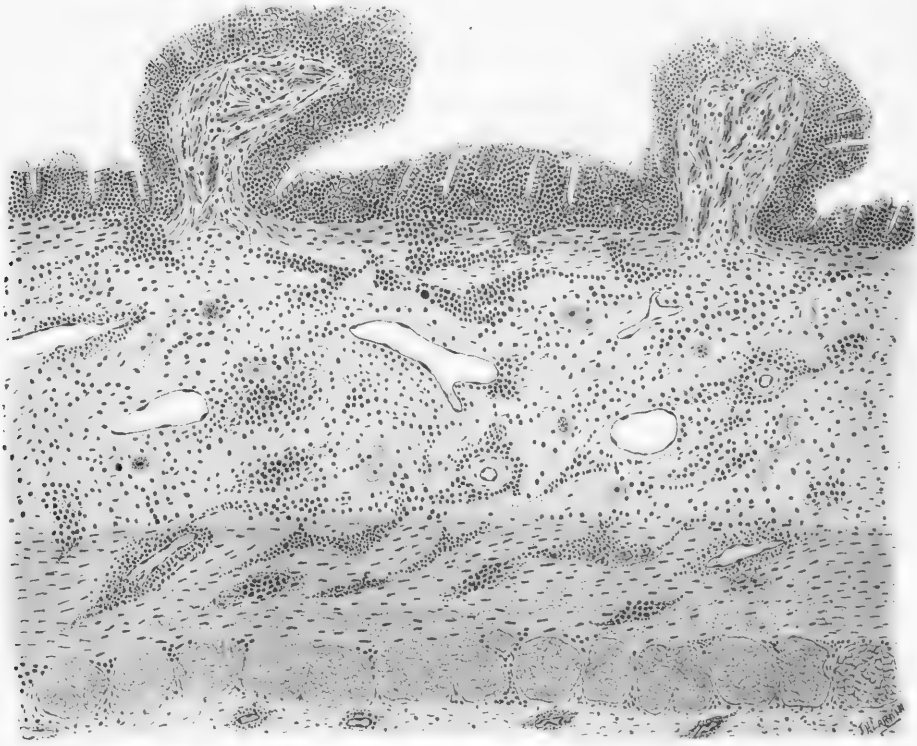
The *adrenals and the mesenteric lymph nodes* presented numerous tubercles and areas of caseation. Here tubercle bacilli were quite abundant. The retroperitoneal glands showed lymphoid hyperplasia and a few microscopic tubercles. Tubercle bacilli were present.

[56] *Bull. de la Soc. anat. de Paris*, vii p. 229.

[57] *Comptes rend. Soc. de biologie*, 1898, p. 1003.

The submucous tissue of the *stomach* showed some round-cell infiltration which in places penetrated into the muscular layers. No tubercle bacilli could be demonstrated within this tissue.

The histological lesions of the intestine are described more fully. (See figure in the text.)



Section of the ileum in its lower third, showing the histological features of the hyperplastic tuberculous intestine in the parts but moderately affected. The topographical and morphological details of two papillomatous processes are seen. (I am indebted to Dr. John H. Larkin for this drawing.)

Intestine.—Naked-eye examination or study with the hand lens of the stained sections of the intestine show two distinct portions, one taking the nuclear dye very strongly and including the mucous membrane and submucosa, the other staining much lighter and made up of the remaining layers.

When examined with the low powers the mucosa shows considerable thickening, about four or five times beyond the normal. In some places this is more marked than in others; it is most striking in the lower ileum and the cæcum. The epithelium generally shows little change; in places it is covered with granular material and broken-down cells, or some of the superficial cells are necrotic. Changes of this nature are, however, strictly limited to the surface. Many sections from the small and large intestine were studied, but nowhere could any solution of continuity of the mucous membrane be demonstrated. The glandular cells present no noteworthy change. The tunica propria, however, shows great increase in thickness owing to massive infiltration. When studied with higher powers this tissue is seen to be almost wholly made up of closely packed, small round cells, taking the nuclear stain deeply. Here and there oval, very few polyhedral, and some spindle cells are sprinkled among the small round cells. So great is this cellular infiltration that the gland structures have been pushed well apart; this has apparently caused diminution of their number. Occasionally wide interglandular spaces may be filled with connective tissue of the adult type in which a few round cells may be found.

The fibres of the muscularis mucosæ have been widely separated in places; at some points the cellular strands pass directly through this layer, having evidently completely destroyed the muscle fibres at these points. On the whole this layer is but moderately increased in thickness.

The papillomatous outgrowths noted at the autopsy present several points of interest. They are directly continuous with the submucous layer and present the same general character of infiltration observed there, but the round-cell accumulation is much less intense and the cellular aggregations more discrete. They are covered by an epithelial layer presenting for the most part the same general features observed in that of the intestine elsewhere. The number of unstriped muscle-fibre bundles distributed in loose and irregular strands is very striking. Just beneath the glandular layer the muscularis mucosæ may be seen as a narrow strand which contains few round cells. Generally speaking, where studied in these ingrowths, this muscle layer is quite compact, usually considerably less abundant than normal and comparatively free from any cellular infiltration. The more central parts of the papillary growths consist of bundles of adult connective tissue, rather loosely arranged, in which a moderate number of round cells are discretely spread. Among and between these connective tissue bands may be seen numerous strands of unstriped muscle tissue, quite variable in size

and compactness. The distribution is erratic. Frequently some round cells may be seen in these strands, to some extent separating the fibres, but this is never considerable. No tubercles, necrosis or giant cells were observed. As the submucosa is approached the muscular tissue becomes less evident, and the fibrous tissue and round cells become more abundant. The muscularis mucosæ becomes thinner, and is continuous with that above the submucosa proper. The whole process becomes less marked as the general level of the intestine is approached.

In the submucosa the accumulations of round cells are rather diffuse, or compact, often enough massed around blood-vessels. In some places this cellular increase completely masks the adult fibrous tissue. However, this is somewhat irregular; in some parts, particularly in the ileum, the increase of adult connective tissue appears to exceed the infiltration with round cells, and in parts of the cæcum and large bowel the same is true. The increase of round cells, however, is the predominating feature in almost all parts of the diseased intestine. In places the submucosa is fully five to eight times thicker than normal. Tubercles were not found. True, in some places, cells of an epithelioid character, intermingled with round cells were present, but these in no wise gave the impression of tubercles or of tuberculous tissue.

The outer muscular layers of the intestine present different appearances in different parts. On the whole they are everywhere thickened in the affected portions of intestine in the cæcum and colon, being three to five times thicker than normal. In the ileum, on the other hand, the degree of thickening is variable. As the cæcum is approached, it becomes greater, and here the muscular coat may be twice as thick as the normal, or even somewhat more. This thickening is due in part to muscular hypertrophy and in part to round-celled infiltration, by far the greater part being attributable to increase in the muscle fibres; the cellular increase plays but a very small part in this thickening of the muscle. Round-cell infiltration is not present in all parts of the intestinal muscle; for instance, in the ileum, except near the cæcum, it is almost entirely absent in this zone. When present the cells are either aggregated in small, irregular areas, when the muscle fibres are pushed apart or destroyed, or arranged along the course of blood-vessels. No increase of adult connective tissue was observed in this layer.

The subserosa is uniformly thickened, partly by diffuse infiltration with round cells and partly by increased adult connective tissue. The thickening is in places three times the normal. The blood-vessels here appear for the most part normal, although often enough round cells exist along their course. Thick bands of fibrous tissue, in which some

round cells are present, pass inward from the subserosa as far as the inner muscle layer, thus separating the bundles of the outer layer to a considerable extent.

The blood-vessels throughout the different layers are generally normal, but some thickening of the coats was sometimes noticeable.

Many sections from different levels were stained by several methods for tubercle bacilli. These bacilli were present in enormous numbers in the epithelial layer of the lower ileum, cæcum and ascending colon, often 20 to 40 in a field (Leitz, oc. 3, oil immersion 1/12). Higher up in the ileum and in the rest of the colon this layer contained only a few or none. The papillomatous outgrowths likewise contained only a few bacilli. In the submucosa tubercle bacilli were present in large numbers in the same regions in which they were abundant in the epithelial zone. In one section of the transverse colon where the infiltration was unusually great I was able to find a few in the outer muscular layer; here the muscle tissue was gone. In this situation the submucosa was quite free from any, so far as I could make out. Many short thick bacilli, which readily decolorized by Gram's method, were also present in the mucous membrane *(Bacillus coli communis?)*.

PATHOLOGICAL ANATOMY.

Although subject to considerable variations, hyperplastic tuberculosis of the intestine presents a fairly definite pathological picture, and on the whole exhibits certain features more or less characteristic of the process. The tumor-mass may attain great proportions and bear a striking macroscopic resemblance to carcinomatous disease, but the microscopic examination reveals the true nature of the disease. The most frequent seat of the affection, as already pointed out, is the ileocæcal region; the rectum, apparently, comes next in order of frequency. Instances of limitation of the process exclusively to the small intestine are very rare. For purposes of distinction and convenience the pathology of the condition is considered in the order of its anatomical distribution.

Ileocæcal Region and Colon.—For the most part located outside the true pelvis in the right iliac fossa these hyperplastic masses begin as small, more or less circumscribed, well-defined growths, rather nodular in form. In its fullest development the disease presents a tumor which may attain the diameter of 8 to 13 cm. Sachs[58] has seen a

[58] References to authors already cited will not be repeated.

specimen measuring 10 by 12 cm. in diameter. More often the size is much less. The process implicates the entire wall of the intestine in an annular fashion; but exceptions to this have occasionally been noted. For instance, Richelot[59] has seen an example in which the growth was situated on the posterior surface of the cæcum.

It is uncommon to find the mass entirely free from adhesions and movable; more often fibrous adhesions bind it to the abdominal wall posteriorly, sometimes to coils of intestine and other surrounding tissues. This may assume such proportions as to render operative interference impossible, as in Koerte's case. Adhesions to the anterior abdominal wall are not the rule. Occasionally the omentum becomes implicated. This has been observed by Routier[60] and Tédenat;[61] or again, as in Czerny's case, the ureter may be involved by the impinging new growth. Coquet has described a case in which the cæcum was adherent to the right kidney by a band of dense fibrous adhesions. In a case reported by Pantaloni the tumor was adherent to the urinary bladder.

In the cæcal type the hyperplastic process, as a rule, is limited to the cæcum and immediately adjoining structures. Rarely, however, quite independently of ileocæcal involvement, the transverse colon (Koenig, Eiselsberg, Esmarch) may alone be implicated. In the case reported by Claude the cæcum and ascending and descending colon were affected, while the transverse colon escaped. In a case observed by Caussade and Charrier the tuberculous process was limited to the sigmoid flexure. Involvement of the entire large bowel may occur (Pilliet and Thiéry);[62] or, as in our own case, the process may affect the greater part of the large and small intestine; this is, however, most unusual.

In the cæcal type, the tumor formed in great part of fibrous tissue infiltrated with a quantity of fat is often further enlarged by the presence of numerous lymphatic glands, some merely swollen, others

[59] Tuberculose du cæcum. Resection partielle; guérison. *Bull. et mém. Soc. de chir.*, 1892, p. 236.

[60] Vide Coquet, op. cit., p. 28.

[61] Vide Itié, op. cit. p. 12.

[62] Contribution à l'étude de la tuberculose locale du cæcum. *Progrès méd.*, 1894, 2. s., xx, p. 408.

actually caseous. A few instances of considerable lymphatic extension have been observed; in one as high as the pancreas;[63] and in another, reported by Auscher,[64] the chain of implicated glands ran up along the aorta, reaching finally to the subclavicular group. Descending glandular involvement has been noted in one instance; Coquet found the glands in the groin and Scarpa's triangle enlarged in one of his cases.

The appendix vermiformis generally escapes the tuberculous process, although it is commonly found embedded in adhesions. Sometimes it presents the ordinary lesions of simple tuberculous ulceration, caseous abscess, or miliary tubercles, or it may be almost completely lost in the new tissue and be represented only by a small finger-like cavity (Itié). Occlusion and dilatation of the lumen have been noted; in one case observed by Thiéry and Routier,[65] the appendix took part in the hyperplastic tuberculous process. In Hartmann's case the appendix was dilated.[66]

The most striking and conspicuous feature of the disease is the extremely thickened intestinal wall, which is often surrounded by a fibro-adipose adherent mass, which sometimes may be peeled or stripped from the intestine proper. "Very far from producing, as in other varieties of tuberculous ulceration of the intestine, a thinning of the walls at this level, this special form is characterized by a very marked thickening of the tunics, and moreover there is deposited around the cæcum a thick and resistant sclero-adipose mass which gives the impression of a neoplasm" (Hartmann and Pilliet). The wall of the intestine feels firm, and is of a whitish or grayish color, occasionally studded with yellow points owing to the presence of caseous tubercles, and somewhat irregular in thickness; here and there points of cicatricial contraction are apparent. The contour is consequently somewhat irregular, at other times almost cylindrical in form. The thickness of the wall varies from 0.5 to 3 cm. In one instance reported by Tédenat the thickness was 5 cm.

[63] Pilliet. Typhlite tuberculeuse chronique. *Bull. Soc. anat. de Paris*, 1891, v, p. 636.

[64] *Soc. anat.*, Nov. 29, 1895.

[65] Cited from Caussade and Charrier.

[66] Tuberculose cæcale. *Bull. Soc. anat. de Paris*, 1892, vi, p. 157.

Narrowing of the lumen at one or more places is almost constant in this class of cases; in most instances this amounts to actual stenosis; the cavity of the cæcum may be almost wholly obliterated. In the case reported by Caussade and Charrier and my own, no such stenosis was present at or near the ileocæcal valve, where it is almost invariable and greatest. The valve itself is increased in thickness and rigid from the growth of new fibrous tissue. In a majority of instances the valve exists only as an obturating membrane. It may be lost in a mass of fibrous tissue, in which a few superficial ulcers with polypoid outgrowths are present (Itié, Obs. I). The stricture may be annular, canalicular, or funnel-shaped, and is usually sufficiently marked to induce chronic intestinal obstruction as one of the clinical features. It may involve the whole length of the diseased gut, but some places are more contracted than others, especially the ileocolic junction. Occasionally the stricture is almost complete; it may be such that the cæcum scarcely admits the little finger. Becker [67] states that in his case water escaped from the constricted bowel only in drops; in Suchier's case it was even very difficult to detect the intestinal lumen.

The stenoses are produced in one of two ways: either by cicatricial contraction of tuberculous ulcers in the mucous membrane or by hyperplasia of the tissues of the wall; certain polypoid growths, already described in the record of my own case, also help such a formation. Multiple strictures are occasionally seen: Frank [68] found two, one in the ileum and the other in the ascending colon; and Czerny one, a short distance from the valve, in the ileum. Out of eighty-one cases analyzed by Conrath, strictures elsewhere than in the cæcum were found seven times. Whenever the strictures are multiple, the intervening portions of gut usually appear normal, with the exception perhaps of ulceration, but the lumen is here generally dilated. Bezançon and Lapointe have seen one case in which four constrictions were present: one just above the cæcum, the second at the hepatic flexure of the colon, the third at the left extremity of the transverse colon, the last above the rectal ampulla. Monnier reported

[67] Ueber Darmresectionen. *Deutsche Zeitsch. f. Chir.*, 1894, xxxix, p. 148.
[68] *Wien. klin. Woch.*, 1892, xxxiii, p. 1846.

another case with multiple stenoses. Strictures are not always present, as is shown by my own case and Claude's (tuberculose hypertrophique non sténosante of this writer).

In the cases with formation of ulcers the condition is merely one of association of simple tuberculous enteritis with the hyperplastic process. Compensatory hypertrophy of the ileum, often associated with dilatation and induration, follows as a result of the resistance to the progress of the intestinal contents. As insisted upon by almost all who have studied this class of lesions, this hyperplasia in the wall of the cæcum is not brought on by the constriction; this is well shown by Caussade and Charrier's case, in which the cæcum was dilated and there was no apparent stricture at any point.

The mucous membrane always presents features of considerable importance and interest. Early in the disease the mucosa may present little change. It is thickened, usually studded with ulcers and some tubercles. These may involve a considerable length of the colon and lower ileum, as in the cases of Pilliet and Thiéry, and Czerny. Cases have been reported in which the mucosa appeared intact macroscopically in well-developed forms of the disease. Such examples have been reported by Sachs, Hofmokl,[69] and Göschel;[70] in my own case no solution in the continuity of the mucous membrane could be made out anywhere, although a careful search was made both macroscopically and microscopically.[71]

Polypoid and papillomatous formations are striking features; they vary in appearance according to the cases. These structures are very constant and constitute one of the most interesting and characteristic of the gross lesions. They are very numerous and quite variable in size, being longest at the margin of ulcers. These structures occur, on the one hand, in the form of small pedunculated ingrowths; and on the other hand, instead of these small masses, or often beside them, there may be large sessile nodules or true polypoid tumors sometimes

[69] *Wien. klin. Woch.*, 1890, iii, p. 878.

[70] Ein wegen tuberculöser Strictur resecirtes Darmstück. *Münch. med. Woch.*, 1895, xlii, p. 251.

[71] In Crowder's case the mucous membrane of the hyperplastic portion was similarly free from ulceration; inasmuch as the bowel could not be examined in all its parts it is impossible to exclude ulceration in the portions above or below the section removed at operation and examined.

reaching the size of a hazelnut (Pilliet and Thiéry). They may have long, slender pedicles. The thickened mucosa, in some cases, is simply thrown into transverse folds; such a condition has been reported by Caussade and Charrier.

In the midst of these ingrowths opaque, white or yellowish white, sharply circumscribed areas appear here and there; these are caseous foci, 2 to 3 mm. in diameter, ordinarily located in the submucosa. These caseous foci, although visible, are usually separated from the lumen by the layer of glands; but they may also communicate with the lumen by a small crater-like opening. In many cases such foci are altogether absent.

Ulcers are rarely absent in all portions of the mucosa; if none are visible it does not necessarily follow that they are absent; they may well be hidden by the folds of the reduplicated mucous membrane. The ulcers are of various sizes and forms, leaving areas of intact mucous membrane between them as in ordinary tuberculous enteritis with ulceration. Sometimes they are reduced to mere crevices in the mucosa but more often they attain greater proportions and are usually annular in form. Occasionally one sees ulcers of considerable size and curious aspect.

Tuberculosis of the mesenteric lymph nodes with or without caseation is the rule. A like affection of the adrenals, as in the present case, is rare. Pulmonary tuberculosis is often secondary to the intestinal lesion in this class of cases.

Rectum.—For years hyperplastic tuberculosis of the rectum has been confused with syphilis of this viscus. Recent studies have thrown considerable light on the whole question. We are particularly indebted to Sourdille [72] for having directed attention in 1895 to this form of disease. Since then Tédenat,[73] Lapointe,[74] and Bezançon and Lapointe have further elaborated the same theme.

In a general way the lesions presented are similar to those observed elsewhere in the intestine and which have already been described.

[72] Rétrécissements cylindriques du rectum d'origine tuberculeuse. *Arch. gén. de méd.*, 1895, i, pp. 531; 697, ii. p. 44.

[73] Vide Aulès, Thèse de Montpellier, 1896.

[74] Lapointe, Traitement des rétrécissements non congénitaux du rectum. Thèse de Paris, 1897.

The hyperplastic process is commonly observed as a cylindrical thickening of a segment of the rectum; caseous masses are not common. Tubercles may or may not be present. The number of cases thus far reported is still small; in 1897 Lapointe had succeeded in collecting but nine reports.

Small Intestine.—Hyperplastic tuberculosis of the small intestine is rare. Here it is not so often a question of those large tumor masses, so easily mistaken for carcinoma; the growth is ordinarily more limited and less voluminous. Nevertheless, the other features of the pathological and clinical pictures are present; even complete stenosis has been observed. Although the lesion of the small intestine may exist without cæcal disease, it is oftener found that the two are concomitant. In a few instances, however, the hyperplastic tuberculous disease has been confined to the ileum, the part near the cæcal end being affected.

In a case reported by Guinard, there were four stenoses; the bowel was thickened, and the lumen "dilated to the point of resembling the stomach." Perhaps the best example of the limitation of the affection to the small intestine is that reported by Pantaloni, where the ileum was affected for a distance of 12 cm., the calibre of the bowel being reduced by one-half.

When the stenosis is marked, the portion of intestine above this point is apt to show hypertrophy of the muscle tissue, and possibly some dilatation. Below the stricture atrophy and thinning of the walls may occur.

MICROSCOPIC LESIONS.

These are essentially an admixture of purely tuberculous and simple inflammatory lesions. The picture necessarily varies much according to the anatomical distribution of the lesions and the character of tissue changes induced by the tubercle bacillus or its products, and secondary infections.

The mucous membrane presents diverse alterations, according to the place examined. It is usually much thickened, sometimes measuring as much as 1 cm. The epithelium when preserved is usually normal. Here and there a few of the cells may have lost their stain-

ing properties. Elsewhere losses are perhaps apparent. The glands of Lieberkühn are absent when ulceration exists, rarely in other places. Many of the cells may have undergone mucoid or cystic degeneration.

The papillomatous outgrowths of the mucous membrane are covered with epithelial tissue, which has been thickened by round-cell infiltration. Tubercles may be found in them or in the submucosa at their base. These polypoid masses are generally continuous with the submucosa, which is often densely sprinkled with round cells; in some specimens the tissue is largely of the adult connective-tissue type. Unstriped muscle tissue may be present in abundance.

The tunica propria is likewise considerably thickened, sometimes as much as four, five or more times beyond the normal. This is due to the same character of cellular infiltration. Sometimes tubercles may be found here. The muscularis mucosæ may be missing here and there where ulceration has penetrated to the submucous layer. The muscle fibres are often widely spread apart or even destroyed by the infiltration of new cells. The thickening is most apparent in the submucosa where the fibrous increase is very marked. Pilliet states that it measured 1 cm. in his specimen; in my own the increase was also very marked. The cell infiltration is by no means uniform in its distribution or histological characters. There is often definite patchy infiltration with intervening areas of less invaded tissue. The cells are mainly of the round type; but spindle cells and much basement substance are likewise frequently to be observed. The wealth of blood-vessels occasionally seen has been studied particularly by Pilliet, and more recently by Chavannaz and Carrière. The latter observers have also noticed the presence of small hæmorrhages.

Tubercles and foci of tuberculous granulation tissue may be present in the mucous membrane; when present they are never very numerous. The majority of tubercles are found in the submucosa. Some may be caseous, with giant cells and round cells; more often the tubercles are mere aggregations of lymphoid cells in which one or more giant cells may be seen. Epithelioid cells are usually absent. The tubercles may be aggregated in small masses of sufficient size to

be appreciated by the naked eye. Many show little tendency to necrotic change; a distinct tendency to fibrous transformation is, on the other hand, apparent. The typical histological features of tubercle tissue are often absent; in lieu thereof there may exist a diffuse embryonal cell infiltration, at times capable of simulating sarcoma (Pilliet); Courtillier applies the name "lymphoid tuberculosis" to the same condition. In my specimen this appearance was well reproduced in many portions.

The muscular coat participates in the general thickening, but to a less degree than the submucosa. The muscle fibres may be widely separated by considerable cell infiltration, the latter located particularly around the blood-vessels. Occasionally tuberculous tissue may be seen in the muscular layers. Routier states that the thickening in his specimen was due largely to caseous infiltration of these layers. Disappearance of the muscle fibres has been observed in one case by Bezançon and Lapointe.

The subperitoneal layer is formed of fibrous bands in which blood-vessels may be seen showing more or less periarteritis and endarteritis; foci of round cells are observed in places. It is particularly this fibrous increase which accounts for the rigidity of the intestine in some instances. Now and then tuberculous foci may be seen, as well as some adipose tissue. Much round-cell infiltration may be present without any definite tubercles (Pilliet and Thiéry). The histological findings in my own case confirm this statement.

The serosa shows few changes in most instances, although in Hartmann and Pilliet's case it was four times as thick as the mucosa.

Most observers agree that the tubercle bacilli in the tissues are scanty; sometimes they may, however, be very abundant, as in Caussade and Charrier's case and in my own. In my specimen the bacilli were limited mainly to the inner layers, being most abundant in the submucosa; a few were present in the tunica propria. None could be demonstrated in the subperitoneal layers or serous coat.

ETIOLOGY AND PATHOGENESIS.

Knowledge of the etiological factors concerning hyperplastic tuberculosis is still unsatisfactory. The whole subject seems to be wrapped

in a certain amount of obscurity. Certain diseases have been regarded as having served as predisposing factors. Thus typhoid fever, the enteritides of infancy, and dysentery are supposed to be particularly concerned in this way. Whether or not they are to be held more responsible than some other diseases which lower the general vitality of the individual is debatable; at all events, future and more extended studies alone can decide this point. The evidence at hand scarcely justifies the conclusion that such a relationship is indisputable.

Sex evidently plays a less important rôle in favoring the development of the disease than Benoit[75] supposes. This observer believes that the disease is more common in women, but Itié's figures of a total of 71 collected cases show 40 men to 31 women. Conrath out of a total of 77 cases, found 36 men and 41 women. The influence of sex, then, does not seem to be very definite. The middle period of life gives the greatest number of cases.[76]

Occupation may have some influence, for instance, such as may lead to frequent traumatism of the right iliac region; too much stress, however, should not at present be laid on this point.

The fact that pulmonary tuberculosis was often absent in this affection, or when concomitant usually secondary in point of time, was noted by those earliest interested in this subject. This and the frequent limitation of the process to the abdominal viscera naturally suggested the primary nature of the intestinal tuberculosis. Further investigation has shown this to be apparently true for a certain number of the observed cases. But even when the clinical history seems clinching enough in this respect, the autopsy often shows "healed tuberculosis" of the lung. For this reason some writers do not concede the primal intestinal origin of the tuberculosis, but regard the bowel lesion as always secondary to some old focus in the lung or

[75] Tuberculose ileo-cæcale chronique; son traitement chirurgical. *Gaz. des hóp.*, 1898, pp. 357, 385.

[76] Crowder, (loc. cit.) gives the following table:

Age.	Male.	Female.	Total.
1 to 10.....	0	0	0
11 to 20.....	4	7	11
21 to 30.....	10	14	24
31 to 40.....	19	10	29
41 to 50.....	3	6	9
51 to 60.....	3	5	8

elsewhere. Such authors think that the occurrence of the form with subperitoneal hyperplasia further reinforces their interpretation; they regard this type as surely indicative of a hæmatogenous origin. As a matter of fact such metastasis is notoriously rare in blood infection. Conrath assumes that a revivescence of latent tuberculosis in mesenteric glands contributes to the peritoneal infection; and thence by extension the subserosa becomes invaded.

So far as I can see, the case which I have herein reported is definitely one of primary intestinal origin in the adult. Not only were evidences of pulmonary tuberculosis entirely wanting, but the character of the visceral tuberculosis in the abdomen tends further to confirm this view.[77]

Primary intestinal tuberculosis is very rare, and particularly so in the adult; the investigations of almost all pathologists clearly show this. A discussion of it, however, is foreign to the purpose of this paper. For the same reason any etiological consideration of the facts relating to intestinal tuberculosis in general has been omitted.

Simple ulcerative enteritis or colitis has been regarded as an important feature in the early genesis of the disease. Itié has particularly insisted upon this point. In his opinion the tubercle bacilli more readily implant themselves upon the mucous membrane under these conditions, and little by little transform an inflammatory process of a simple nature into one of a tuberculous character. The belief of Hartmann, Pilliet, and Benoit that secondary infections induce some of the changes described and contribute in some measure to the production of the lesions met with in this class of cases, it seems to me, will in time receive confirmation in the results of investigations in this direction. The extent to which these factors may be regarded in the pathogenesis of the disease is uncertain; they probably represent only two of the many classes of conditions which one might conceive to be of similar significance. That previous ulceration is not always necessary is shown by the case of Kirkoroff[78] and my own; in neither

[77] The first case reported by Crowder, (loc. cit., p. 671), may belong to this class; however, as no post-mortem control exists for this case objection may very properly be raised to its acceptance as such. Clinical signs, alone, invite too many errors to be accepted in this consideration.

[78] Kirkoroff. Tuberculose de l'intestin. *Arch. russes de path.*, Oct. 1898.

of these two cases was any solution of continuity demonstrable. In the case reported by me this was true for both the naked eye examination and the microscopic study. It is quite true that although no such solution could be established, one or more minute losses of tissue might exist and escape detection. But the passage of bacteria through the apparently uninjured mucosa is not wholly inconceivable; experimental investigations by Dobroklonski [79] and the writer have shown that tubercle bacilli might easily enough traverse the healthy mucosa of the intestine of rabbits (leaving it, as far as the most careful studies show, intact) and incite tuberculosis of the mesenteric glands.

The frequency with which the lesion is localized in the cæcum and rectum is probably explicable by the fact that stasis is favored in these regions, giving opportunity for implantation of the tubercle bacilli on the mucosa.

The chronicity of the disease and low grade of inflammation observed have been explained in various ways. For my own part I interpret the phenomena by assuming an infection with attenuated tubercle bacilli. Whether this is brought about, as Hartmann believes, by the intervention of secondary infections, is difficult to say. I fancy, however, that these invasions, when they occur, may have more to do with the production of simple inflammatory lesions than with an attenuation of the tubercle bacilli. The small number of bacilli present in the tissues has also been held to explain the chronic course of the process.

It is possible that bacilli of low virulence and elaborating but small quantities of toxic material irritate the tissue only sufficiently to stimulate fibrous hyperplasia, the irritant being insufficient to produce necrotic lesions. I certainly think that there is evidence for this in the case of the tubercle bacillus and *Bacillus pyocyaneus*.

Although the process is a remarkably slow one, progression finally leads to tumor-formation with resulting intestinal obstruction in a large proportion of the cases; from this the patients sink gradually to the fatal issue, unless surgical intervention is invoked. In others in which no stenosis is present some terminal infection usually carries the patient off.

[79] De la pénétration des bacilles tuberculeux dans l'organisme à travers la muqueuse intestinale. *Arch. de méd. expér. et d'anat. path.*, 1890, ii, p. 253.

Abscess formation is not common; fistulæ have been present in a few cases. Extension of the tuberculosis to the peritoneum is similarly rare. Whenever the disease progresses, it is by way of the lymph channels rather than by the blood current.

SYMPTOMATOLOGY.

Wide variations in the clinical picture are met with in different cases, determined largely by the location of the tumor-mass and the point of stenosis. The symptomatology of hyperplastic tuberculosis of the small intestine and ileocæcal region will be considered separately from that of the rectum, the clinical features of the process in these situations being sufficiently distinct to permit of separate treatment.

Hyperplastic Tuberculosis of the Small Intestine and Ileocæcal Region.—The onset is indefinite; sometimes it seems to follow some acute disease in which intestinal lesions were present, such as gastro-enteritis, dysentery, or typhoid fever. The earliest symptoms are generally referable to the gastro-intestinal canal: dyspepsia, vomiting, and some pain in the abdomen. Abdominal pain is one of the most constant symptoms at the outset, sometimes coming on after the taking of food, but usually independent of such. Colicky pains, with or without vomiting, may suddenly attack an individual in apparently good health. The abdomen may be tympanitic, with tenderness most noticeable on the right side; shooting pains through the thighs (Bouilly) may also be present. Later, or perhaps concomitant with the gastric derangement, attacks of diarrhœa and constipation often alternate, with varying prominence of the one over the other; early in the disease the former is the rule until stenosis develops. Persistent diarrhœa, in some cases without constipation at any time, has been observed (Pilliet). Constipation may be the only symptom from the start until the disease is well advanced. When marked, mechanical obstruction has probably already occurred. Hand in hand with the development of these symptoms there will be noticed loss of strength and weight, and often a slight evening rise in the temperature. These may be the only symptoms in the early part of the disease or, as sometimes occurs, throughout the illness.

The intestinal discharges present no characteristic features; at one time they may be quite normal, at another glairy and mixed with pus. Melæna has been observed in some cases. Icterus has also been noted in one case (Coquet).

With time the abdominal crises become accentuated and the weakness very great. Some patients suffer from recurring colic, accompanied by vomiting and constipation. The area of greatest tenderness is often the right iliac fossa. Meteorism is common during these attacks.

So far as I know, my case is the only one in which pigmentation of the skin has been observed; whether or not this is due to the adrenal affection, it is difficult to say. A similar grade of adrenal tuberculosis, in my experience, is often seen without any such pigmentation.

The clinical picture in the early phases of the trouble is often so indefinite that diagnosis is impossible. As the disease progresses during months or years, other symptoms of a more definite nature make their appearance. By this time signs referable to intestinal obstruction will usually draw attention to the abdominal lesion.

With the symptoms of obstruction a mass is generally noted at the point of involvement, which is usually in the right iliac fossa. From this time on the clinical picture is more and more definitely that of chronic intestinal obstruction, such as one finds in carcinoma of the same parts. This is too well known to necessitate reiteration here. If not already present, pulmonary tuberculosis may develop as a complication.

Physical Signs.—Inspection of the abdomen may show more or less distension—a condition associated at first with the abdominal crises but later becoming permanent. When there is much pain the abdomen may be contracted. The skin is usually normal. Exceptionally the size of the mass is sufficient to be seen on inspection; thus Tédenat reports one instance where it was as large as a fœtal head. A few cases show fistulous tracts, located most often in the right iliac region; openings of this kind may be found also in the vicinity of the anus. Benoit speaks of the occasional occurrence of an infiltration of the abdominal wall in this region with ulcerating fungoid growths, simulating sarcoma.

Tenderness is generally elicited by palpation wherever the growth is situated. When localized in the cæcum the limits of the tumor appear definite enough below and externally; below, the mass appears to terminate just above Poupart's ligament; laterally it lies just within the iliac crest. It rarely extends to the median line. Above, the termination may be abrupt; or the growth may continue as a cylindrical mass running up for some distance. Sometimes the decrease in size is very gradual. Esmarch, Koenig and Eiselsberg have each reported a case in which the upper limit was felt in the region of the umbilicus; here, however, the transverse colon was the seat of disease.

When the abdominal muscles are lax the growth may be felt as a firm, nodular mass, in which one can often with difficulty get lateral movement. The anterior abdominal wall, on the other hand, may be freely moved over the fixed growth.

Percussion signs are very variable and unreliable. Dullness is usually present directly over the tumor; but sometimes the note is tympanitic. In women vaginal examination may or may not be of value; rectal examination is often more satisfactory.

Rectum.—In its advanced form hyperplastic tuberculosis of the rectum presents symptoms analogous to those of other rectal stenosing diseases. Hæmorrhages from the rectum have been noted in a large proportion of the cases. They may appear from the very start, when the very earliest symptoms of inflammation begin. The bleeding may occur at defecation, or in the intervals. The blood is pure or mixed with mucus. As the disease progresses the rectal discharges change in character; instead of blood, a thick, glairy material is passed. Pain and a burning sensation in the rectum are common. Diarrhœa is sometimes present. At a later stage pain and tenderness are developed between the anus and coccyx; the sphincter ani becomes contracted, and the rectal mass is covered with many soft, pedunculated or sessile vegetations which bleed very readily. In the early stage of the affection, Itié lays a good deal of stress upon the presence around the anus of small bleeding tumors of uncertain nature.

After a period extending over months or years signs of stenosis develop. Greater and greater mechanical obstruction to the passage

of fæces is offered, and the clinical picture resembles that of syphilitic or malignant disease of this part. Perianal abscess and ulceration are sometimes formed. Examination per rectum is always painful. One or another of the divisions of the rectum may be the seat of the lesion; most often the last part of the rectum is the portion involved. The diminution of the lumen may be so great as not to permit introduction of even a sound. The entire circumference of the rectum is often thickened.

TREATMENT.

In the light of recent knowledge concerning cæcal disease, it seems reasonable to conclude that most of the resected cases of cancer of this region reported without careful microscopic examination as cured were instances of hyperplastic tuberculosis. The treatment of the condition is obviously surgical; extirpation of the diseased tissue promises good results in a fair proportion of cases. Nové-Josserand reports a recovery following simple laparotomy. Those interested in the surgical phases of this subject, including operative technique, may be referred especially to Itié's thesis and the articles by Benoit and by Conrath.

A CASE OF MULTIPLE MYELOMA.

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Plates V and VI.

During recent years there have appeared several descriptions of a peculiar condition in which simultaneously several bones become the seat of a new growth which often erodes through the cortex and pushes aside neighboring tissues, but which never metastasizes into other organs. The results of the observations of such so-called multiple myelomata and related diseases have been well summarized and discussed by Hammer,[1] Winkler,[2] Wieland,[3] Paltauf,[4] and others, and it is not necessary to repeat this discussion. In brief, the conclusions are as follows: The tumors are distinguishable from other malignant tumors by their mode of growth and the absence of metastasis—from myelogenic sarcomata in particular by their multiplicity and the uniformity of their component cells, giant cells and spindle cells being practically absent. The resemblance of the myeloma cells to those of the bone-marrow and especially the great macroscopic resemblance of the tumors to the adjacent bone-marrow, from which they can scarcely be delimited, have given rise to the opinion that they spring from some of the bone-marrow cells, although Wieland attempts to disprove this. It has been suggested that the process is of an infectious nature. Comparisons with pseudoleukæmia and leukæmia seem to show that they may be readily distinguished.

Recently Wright[5] has described in the cells of such a tumor a

[1] Virchow's *Archiv*, 1894, cxxxvii, p. 280.

[2] Virchow's *Archiv*, 1900, clxi, p. 252.

[3] Primäre multiple Sarcome der Knochen. Inaug.-Diss., Basel, 1893.

[4] *Ergebnisse der allgemeinen Pathologie u. pathologischen Anatomie.* Herausgegeben von Lubarsch u. Ostertag, 1896, iii, 1, p. 676.

[5] Contributions to the Science of Medicine, dedicated by his pupils to William Henry Welch, p. 359. Baltimore, 1900.

resemblance to plasma cells and speaks of the new growth as a plasmoma.

The cases have been described under the most various titles, but there seems to be a well-defined condition easily distinguishable from the endotheliomata and sarcomata of bone for which the name myeloma is most fitting, a condition which Virchow prophesied,[6] although at that time no case had been published.

The description of the following case may be permitted as an addition to the still rather limited series reported. The clinical features, including the occurrence of albumosuria, have already been described by Dr. Hamburger in the *Bulletin of the Johns Hopkins Hospital*, 1901, xii, p. 38. They consisted in the spontaneous occurrence of fractures of several of the bones followed by the appearance of definite soft tumor masses over various bones. There was no marked anæmia—red corpuscles, 3,548,000; leucocytes, 4500; hæmoglobin, 52 per cent, with normal relations among the different varieties of white corpuscles. Albumosuria was definitely determined.

The autopsy record, copied in brief from the protocol, is as follows:

Anatomical diagnosis.—Multiple myeloma: tumor masses in femur, ilium, clavicle, sternum and scapula, with pathological fractures. Tumor mass protruding from skull. Chronic nephritis. Arteriosclerosis. Myomata uteri. Healed tuberculosis of lungs.

Body is that of an emaciated old woman. The right leg is shorter than the left by about 3 cm., and in the trochanteric region there is a tumor mass, at which point there is excessive mobility of the femur. Tumor nodules are to be felt over the left scapula, the left clavicle, and over the vertex of the skull, where the scalp is tensely stretched over the large, soft, almost fluctuant tumor.

The organs throughout showed evidences of senile atrophy, this being especially marked in the heart and liver. The lungs present old scarred tuberculous lesions at the apices. In the uterus there were several myomatous nodules. Nowhere in the organs was there any evidence of the formation of tumors such as those to be described in the bones.

On removal of the sternum it was found to contain at the point of insertion of the second and third costal cartilages a tumor mass which,

[6] Die krankhaften Geschwülste, Bd. ii, p. 7, Berlin, 1864.

being very soft, allowed free movement of the two parts of the sternum upon one another. The left clavicle was much enlarged at its sternal end, the bone being apparently distended by the tumor mass within, for the cortical portion was very thin and could be compressed by the fingers. On sawing through the bone lengthwise the cancellous bone was found to be much rarefied and the cortical portion very much thinned—the marrow was almost entirely replaced by the tumor mass, which extended quite to the acromial end.

The right clavicle showed evidences of a healed fracture, the portions having united in a somewhat abnormal position, so that a slight angular deformity existed. The marrow of this bone also showed tumor masses, which did not, however, cause any extensive erosion of the bone.

From the spinous process of the left scapula there arose a soft tumor mass which on section was found to have eroded and replaced a considerable portion of the bony process. None of the cortex or cancellous bone tissue was to be discovered in this one. The ribs were not involved. Unfortunately the vertebral column was not sawn through, but there were no evident tumor masses visible from without. The right ilium was completely eroded through in its median portion by a large soft mass which had destroyed the whole thickness of the bone and which projected both ways—into the pelvis under the iliacus muscle, and outward under the muscles covering the outer surface of the ilium. The hip-joint on this side showed no abnormality, but in the intertrochanteric region a large tumor mass sprang from the marrow of the femur. At the upper end of the shaft of the femur there was a fracture, the shaft being displaced upward. On sawing through the bone at this point the intertrochanteric region was found to be extensively involved in the new growth, which extended into the adjacent tissues. The cancellous bone was almost entirely destroyed and the cortex much atrophied and roughened internally. For a distance of about 5 cm. the cavity of the shaft of the femur was invaded, the yellow marrow being pushed ahead and fairly sharply limited from the dark purple new growth. The bone marrow was atrophic and œdematous, greyish pink and moist in appearance, and sunken below the level of the cut surface of the invading tumor. The left femur showed no evidence of tumor formation.

Removal of the large mass at the vertex of the skull revealed a large aperture in the skull, the edges of which were very ragged, as if gnawed away, with here and there loose spicules of bone lying in the soft tumor mass which evidently sprang from the marrow cavity. This tumor mass spread itself between the cranium and the dura for a short dis-

tance, and, completely filling the aperture in the skull, projected outward to form the large soft mass felt under the scalp.

No other tumor nodules were to be found so far as it was possible to examine the bones.

These growths presented everywhere the same appearance. Everywhere they evidently sprang from the marrow of the bone from which they were not by any means sharply demarcated. Only where the tumor seemed to invade the yellow marrow of the shaft of the femur was the outline sharp, but even there the microscopical examination showed evidences of the presence of tumor elements far past this outline. Where the red marrow of the short bones formed the point of origin, the outline was not nearly so sharp. The well-defined tumor masses were perhaps somewhat firmer than such a mass of bone marrow would be. They varied somewhat in consistency however. In general they were soft; some of the larger were almost diffluent and flattened out when cut and laid out on a pan. Others were less soft, and in some parts the gelatinous pulpy consistency gave way to a fair degree of firmness. In color there was also considerable variation. The greater part of the masses was of a deep red color, perhaps even darker than that of the normal red bone marrow, but showing everywhere a greyish tint. Usually lines and streaks of grey were to be seen throughout this deep red, and in nearly all the masses definite nodules of firmer consistency and of greyish white color were found. At some points there was a slight yellow opacity.

Microscopically, the various authors have emphasized the regularity in form and size of the cells, and Wieland has adduced this as a distinction from the myelocytes. Nearly all writers have thought the tumor cells to be derived from some cell or other of the bone-marrow. Wright alone considers them to be plasma cells or closely related cells at least, to explain which he states that plasma cells are present in the bone-marrow. The results of attempts to determine the histogenesis of the cells in this case will appear from the following description of the microscopical appearances.

The tumor masses present in sections a remarkably homogeneous appearance (Plate V, Fig. 1). There is, as described in practically all of the other cases, a delicate stroma with rather wide meshes in which lie innumerable rather large round cells. These are not in intimate connection with one another, but lie singly and loose; some-

times where their number is very great they are somewhat compressed into a polygonal form, but in general they are fairly regularly rounded; they vary slightly and may be elongated or pear-shaped or even notched. The nucleus is large, round and vesicular, sometimes lying eccentrically. The protoplasm presents a rather ragged granular appearance. Blood-vessels exist throughout the tumor and are indeed rather numerous. The smaller ones lie in very intimate contact with the tumor cells, their walls being merely a single layer of endothelium. Connected with these and the coarser strands of the stroma are exceedingly fine filaments of connective tissue which run in between the cells. Everywhere scattered quite without order through the tumor mass and among the tumor cells are numerous red blood-corpuscles, which are quite well preserved. These evidently give the dark red color to the tumor masses, being absent or present in only very small quantity in the translucent greyish white nodules described above.

More careful examination of the characteristic cells of the tumor was made by the aid of various methods.

The cells are distinctly of one type, although variations in size and general appearance occur (Plate V, Fig. 1). The well-preserved cells vary in diameter from 13-21 μ. Perhaps their size is best shown by the camera drawing of a number of them where they can be compared with red corpuscles. Fig. 2 (Plate V) shows their relation in size to other well-known cells, B being tumor cells, A plasma cells, and C myelocytes. Their outline is in general smooth and sharp, and there are no processes or evidences of intimate union with adjacent cells. Ordinarily they lie quite free side by side in the spaces in the stroma, generally separated from one another by interspaces in which red corpuscles may be found.

The nucleus is quite large and rounded, and of a definitely vesicular type. It may be situated at any part of the cell, often near one extremity, when, as so frequently occurs, the cell has an elongated pear shape, this perhaps suggesting the appearance of a plasma cell. It is not at all uncommon to find two or three nuclei in one cell, and indeed four round and quite separate nuclei have been observed in a single well-preserved rounded cell. Each of these nuclei has the vesicular type and other characteristics to be described for the single ones (Plate VI, Figs. 3 and 5). In almost every intact nucleus a sharply outlined shining round nucleolus can be made out; its size is best seen in the drawings, all of which are made accurately to the same scale with the camera lucida. This nucleolus can be best seen in sections stained with carbolic fuchsin or safranin, where it stands out as

a glistening red refractive body, or with carbolthionin, where it stains bright blue and is very conspicuous. It is also to be seen in hæmatoxylin specimens, although somewhat masked by the adjacent tingible substances in the nucleus; stained with polychrome methylene blue it appears rather paler and greyer than the remaining nuclear structure.

Beside the nucleolus the nucleus contains points and strands of chromatin arranged sometimes in a somewhat radial way, sometimes more irregularly. In dried smears from the tumor mass fixed with heat and stained with Ehrlich's triple stain, the nuclei present a peculiar appearance. They look large and flattened out and stain in general a homogeneous pale blue. The nucleolus is not especially evident; it takes here a rather paler color than the remaining nuclear substance. The pale blue color does not, however, appear throughout the nucleus, for there are irregular spaces which show no blue but a reddish stain. One gets the impression that the nucleus is composed of ramifying bands of blue staining substance in the meshes of which the nuclear substance does not stain or stains only like the general protoplasm of the cell (Plate VI, Fig. 7). In this way a certain similarity exists between the staining properties of these cells and of the myelocytes. The nuclei of megaloblasts are also sometimes seen to show the same curious appearance. In the myelocytes this lacunar condition of the nucleus is quite visible, although it is somewhat masked by the presence of the granules. When the smear is stained in hæmatoxylin and eosin, however, it is very plainly to be seen. A smear from normal red bone-marrow shows many cells in addition to the granulated myelocyte, which, except in the fact that neutrophile granules are absent, resemble the myelocytes exactly, and the nuclei of these show very definitely this arrangement of fields of blue and pink.

The protoplasm appears in sections rather ragged and granular. The granules are not very sharply outlined; they are not so minute as the neutrophile granulations of polynuclear leucocytes or of myelocytes, nor so large and definite as the eosinophile granulations. Indeed one can scarcely speak of definite sharp granules, but rather of a somewhat granular appearance of the protoplasm. The raggedness is added to by the frequent occurrence of minute vacuole-like spaces, which sometimes become quite prominent. Winkler found in his case a fatty degeneration of the tumor cells and the tiny spaces in the protoplasm of these cells do suggest the presence of fat. Formaline specimens treated by Marchi's method, however, show no evidence of it.

In the sections stained with the triacid Biondi-Heidenhain mixture the protoplasmic granules appear, but they take no definite coloration

different from that of the adjacent protoplasm. In smears stained with the Ehrlich triple stain the whole protoplasm has a pale pink coloration. *No specific granulations are to be seen.*

In sections as well as in smears stained with the polychrome methylene blue of Unna or the alkaline methylene blue the protoplasm takes on only the palest greenish grey coloration; there is nothing of the specific staining described by Unna and others for the plasma cells. With polychrome methylene blue and eosin the protoplasm stains with eosin.

The relation of these cells to the other normal cells from which they might possibly arise is therefore about as follows: In size they greatly exceed the plasma cells, but agree fairly well with the myelocytes and non-granular cells resembling myelocytes found in the bone-marrow. With polychrome methylene blue, etc., they do not show the reaction typical of the plasma cells; on the other hand, their protoplasm, although in its raggedness it does resemble the "granoplasma" described by Unna for the plasma cells, shows none of the specific granulations characteristic of the myelocytes. The presence of a nucleolus must be admitted for all these various types of cells, so that it is of no help in determining such relations. The cells of the myeloma and the myelocytes and non-granular cells of the bone-marrow have in common, however, the peculiar lacunar structure of the nucleus, as seen in dried smears, which H. F. Müller[1] describes as follows: "With adequate magnification one sees in the myelocytes a remarkable nuclear structure; one finds often nuclei in which definite clear fields are visible. These may be in part nuclear substance, but in many such nuclei these fields seem to represent the cell substance which stretches itself into pre-existent holes or pores in the nucleus." And then again, "there is a large round or oval nucleus limited by a thin chromatin wall which shows frequently more or less numerous larger and smaller clear areas, which are often plainly seen to be definite apertures in the nucleus through which the cell substance extends into the interior of the nuclear body."

This structure seems so peculiar that its occurrence in these various cells at least indicates their close relation to one another. The descrip-

[1] *Deutsches Archiv f. klin. Med.* 1891, xlviii, p. 57.

tions and figures of plasma cells in the papers of Unna,[8] Jadassohn,[9] Marschalko,[10] Justi,[11] Krompecher,[12] and Councilman [13] give no hint of such a structure in the nuclei of these cells.

The myeloma cells are apparently separated from the myelocytes by the absence of the characteristic neutrophile granulations. An examination of a bone-marrow smear, and more especially of a smear from actively proliferating bone-marrow, will convince one of the great variations in the abundance of the granules which occur in these cells. In a recent paper on the relation of the myelocytes to leucocytosis, Rubinstein [14] describes the transitions which take place in the development of myelocytes from smaller cells whose protoplasm is quite free from granules. These young myelocytes reach quite the size of the adult myelocytes before the granules appear, which they do gradually a few at a time. The resemblance then between these non-granular myelocytes, as they may perhaps be called, and the myeloma cells is most striking, and suggests most strongly the origin of the myeloma from these characteristic cells of the bone-marrow in one or other stage of their development.

Further evidence of this close relation is given in the abundant presence of the tumor cells in the marrow adjacent to the tumor masses, where they take on exactly the arrangement of the myelocytes among the fat cells and are intermingled with the occasional eosinophile cells. Indeed if, in a large section, we pass gradually from the relatively normal marrow toward the tumor, we find a gradual and insensible transition, the myelocytes being replaced entirely in time by the tumor cells, which become more and more densely arranged, forming finally definite nodules. Among the trabeculæ of the cancellous bone this consolidation of the cells which have the position and form of myelocytes into solid strands in direct continuity with the tumor mass is very convincing evidence of the direct relation between the tumor and bone-marrow cells.

[8] *Monatshefte f. prakt. Dermatologie*, 1891, xii, p. 296.
[9] *Berliner klin. Wochenschrift*, 1893, xxx, p. 222.
[10] *Archiv f. Dermatologie u. Syphilis*, 1895, xxx, p. 3.
[11] Virchow's *Archiv*, 1897, cl, p. 197.
[12] Ziegler's *Beiträge z. path. Anat.*, 1898, xxiv, p. 163.
[13] *Journal of Experimental Medicine*, 1898, iii, p. 401.
[14] *Zeitsch. f. klin. Med.*, 1901, xlii, p. 161.

Various alterations in the appearance of the tumor cells, which may perhaps best be interpreted as degenerative changes, frequently occur. Division of the cells by karyokinesis has not been once observed in this case, although such nuclear figures were carefully sought after. As described above, however; many of the cells contain more than one nucleus—sometimes as many as four—and in such cases the cell is generally larger than the average, in some instances reaching a great size (Plate VI, Figs. 3 and 5). These multiple nuclei are generally rich in chromatin and stain very deeply. They are often quite irregular in outline and occasionally they are seen to be in connection with one another by a band which may be so thin as to appear as a mere filament of nuclear substance. This is very probably to be considered as evidence of amitotic division—a process demonstrated by Nedjelsky [15] in Marchand's laboratory to be not uncommon in various tumors (Plate VI, Figs. 4 and 6).

Often the nucleus of a tumor cell of average size and with the general appearance of being well preserved shows a dense clumping of its chromatin into several rounded deeply staining solid masses which lie then against the limiting membrane of the nucleus (Plate V, Fig. 1). Again, other cells show a tendency toward disintegration of the protoplasm which breaks up into fine granular masses. The nuclei of such cells often appear very pale. Finally, certain cells, sometimes of nearly the average size but generally much larger, show the presence of vacuoles of greater or less size in their somewhat swollen looking and disintegrated protoplasm. The nuclei are pale and crowded to one side, and in the vacuoles are rounded bodies showing transitions in size and appearance from very small highly refractive round bodies to rounded masses of the size of a red corpuscle or slightly larger. These are denser and more solid and refractive than the red corpuscles (Plate VI, Fig. 8). With the Biondi-Heidenhain stain, with which they show best, they stain a bright orange-yellow or brown; with polychrome methylene blue they take little or no stain, except for a rounded denser fleck in the centre, which, visible by its slight variation in color in the Biondi-Heidenhain

[15] Ziegler's *Beiträge zur path. Anat.*, 1900, xxvii, p. 431.

preparation, stains pale blue here. Such cells are often much disintegrated and the inclusions are sometimes found free. These bodies are apparently very similar to the cell inclusions so commonly found in carcinomata and other tumors, as to which there is at present such active discussion.

The tumor mass as described above contains in the interstices between the cells very numerous red blood-corpuscles in a very well-preserved condition. There is very little evidence of any breaking down of the red corpuscles—hardly any deposit of hæmatoidin in the tissues, which would certainly be present if the presence of the blood were due to actual hæmorrhage. Red corpuscles are found scattered in considerable numbers among the myelocytes and other cells in the normal bone-marrow, however, and it seems probable that the condition here is analogous. The walls of the blood-vessels in the tumor are nevertheless of extreme thinness and extravasations might readily occur.

So also tumor cells are quite frequently found inside these blood-vessels lying among the red corpuscles (Plate V, Fig. 1), although an examination of the circulating blood a few days before the death of the woman showed only one or two doubtful myelocyte-like cells among a great number of leucocytes, the varieties of which were those of the blood in practically normal relations.

In conclusion, then, we have in this case multiple new growths from the bone-marrow, not very sharply delimited from the marrow and showing very gradual transitions into it. The cells have the form and general characters of the bone-marrow cells, lacking the specific granules of the myelocytes but possessing the peculiar nuclear structure found in the myelocytes and their formative antecedents. They differ in essential particulars from the plasma cells, and in view of these facts and the fact that they largely replace the myelocytes in the marrow in the neighborhood of the tumor, there being no sharp boundary between the myeloma-like marrow and the myelocyte marrow, we may consider them directly related to these cells and probably derived from the large non-granular forerunners of the myelocytes.

Degenerative changes, the presence of numerous cell inclusions, and the abundance of red blood-cells scattered in the tumor mass have been noted. The etiology of the affection remains obscure.

DESCRIPTION OF PLATES V AND VI.

PLATE V.

Fig. 1. Portion of a section of the tumor from ilium. In the centre a thin walled blood vessel in which a tumor cell lies among the blood corpuscles. Several of the cells show the condensation of the chromatin into solid masses. Among the tumor cells are many red corpuscles.

Fig. 2. *A* Plasma cells, *B* cells from the tumor, *C* myelocytes from normal bone marrow. The drawing is intended to show merely the relative size of the cells and of their nuclei.

PLATE VI.

Figs. 3 and 5. Large tumor cells with multiple nuclei.

Figs. 4 and 6. Similar large cells in which the peculiar form of the nucleus is suggestive of amitotic division.

Fig. 7. Cell from myeloma as it appears in a heated smear stained with Ehrlich's triple stain. The lacunar appearance of the nucleus is exactly that seen in the myelocyte and its related cells.

Fig. 8. Several large somewhat degenerated cells with rounded inclusions lying in vacuoles in the protoplasm—one cell of the average size and appearance found in the tumor is introduced here for comparison.

All the figures except Fig. 7 are drawn with camera lucida to the same scale.

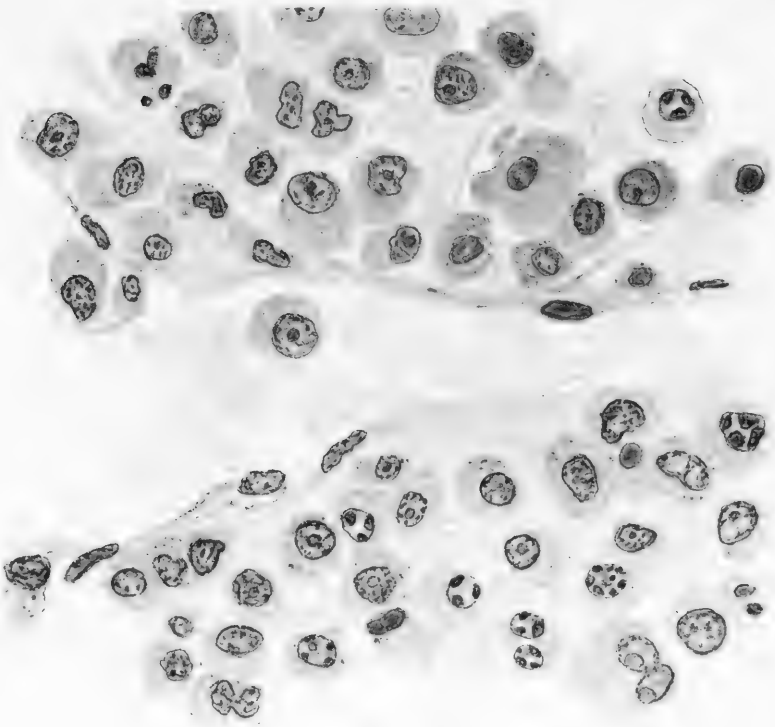


FIG. 1.

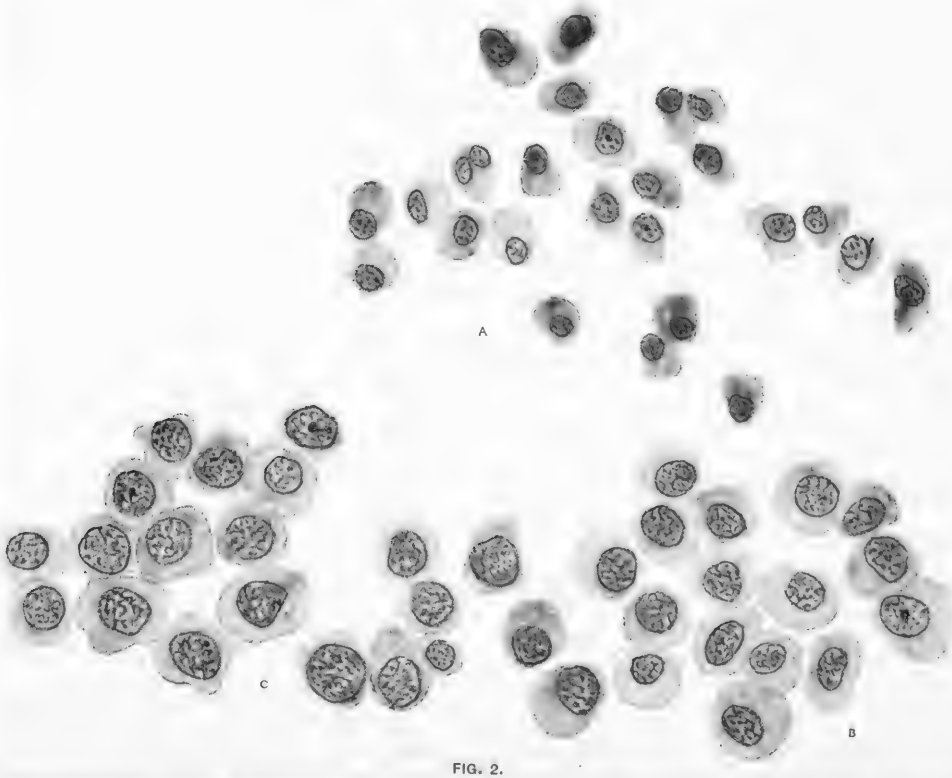


FIG. 2.

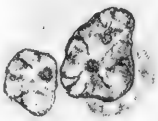


FIG. 3.

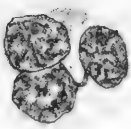


FIG. 4.

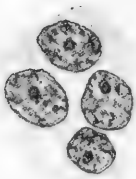


FIG. 5.

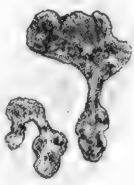
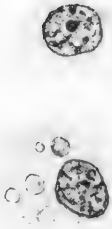


FIG. 6.

FIG. 7.



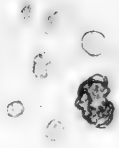


FIG. 8.

ACUTE EPIZOÖTIC LEUCOENCEPHALITIS IN HORSES.

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PLATES VII AND VIII.

A recent epizoötic among horses in Maryland, resulting in the death of a great many animals after a very brief illness, has led to the post-mortem examination of a number of such animals with results which seem worthy of note.

The disease, which is popularly known in this region and probably elsewhere as "cerebrospinal meningitis," presents fairly characteristic symptoms, which when the cases appear in epizoötic form lead readily enough to a diagnosis. Prodromal symptoms are not always present, although in many cases a general malaise may be noted before the acute onset. The acute symptoms are in general such as may be referred to a cerebral lesion. There may be drowsiness associated with an impairment of sight. Partial or complete paralysis of the pharynx is often observed; twitchings of the muscles of the shoulders and thighs, coldness of the extremities, and a general condition of unsteadiness and weakness with a tendency to walk to one side or a staggering, objectless gait, arise early in the disease. The pulse is usually normal; the temperature varies between 96° and 103° F., an elevated temperature usually indicating a secondary complication.

The horse may then become gradually comatose, responding slightly or not at all to stimuli and soon sinking to the stable floor not to rise again. In other cases there is a wild delirium, the animal rearing about and rushing blindly against obstacles, and this may be followed by exhaustion and the comatose condition.

The duration of the disease varies from a few hours to a week, the

average being perhaps 72 hours. Horses which recover are said to become "dummies"—animals with a permanent cerebral lesion and defective intelligence.

The following pathological report is based on the examination of four brains, brought to the laboratory by one of us (Buckley), from animals dying in the acute stages of the disease. There was also one brain from a horse which was said to have had the disease some time before and to have recovered, dying afterward from some other cause.

Of the four brains from acute cases, three were hardened in formalin and one was fresh. Of these, none showed any signs of the presence of an inflammation of the meninges; there was at most a trifling hyperæmia of the pia mater. The surface of the fresh brain showed no localized or circumscribed alterations in color, but the normal level of the convolutions was not everywhere preserved. In the frontal region on each side, anterior to the motor region of the cortex, there was a slightly depressed area which was softly fluctuant, but not marked out by any superficial hyperæmia or discoloration. On cutting through this brain a glairy fluid with small granular pulpy masses of whitish tissue flowed out from the softened area, and the rather thin roof composed of the meninges with the grey cortex collapsed over the cavity thus left. The lesion seemed almost entirely limited to the underlying white matter, which throughout an irregular area, perhaps 2 x 1 cm. in diameter in the left hemisphere, and a symmetrically placed focus 5 cm. in diameter in the right, was completely softened into a diffluent mass made up as described of shreds of softened, necrotic-looking, greyish white brain substance lying in a greyish, glairy or somewhat glutinous fluid. The portions of the brain substance forming the lining of the cavity could be fairly sharply outlined from the adjacent more normal white matter by its softness and raggedness, by its mottled greyish and yellowish opacity with translucent areas, and by the presence of numerous minute hæmorrhages sprinkled through it and adding to its mottled appearance. The remaining brain substance showed no apparent abnormality. The lining of the cerebral and olfactory ventricles was not congested nor inflamed. The blood-vessels were carefully traced and showed no thrombotic occlusion at any point.

Examined microscopically in the fresh state, the softened material showed necrotic cells and cell fragments of various forms; there were also beaded elongated fibrils thought to be axis cylinders with adhering myelin droplets. But few nuclei were found. No bacteria were found by the ordinary staining methods.

Cultures were made aërobically and anaërobically on various media—agar, glycerin agar, blood-serum agar, hydrocele-fluid agar, etc.—but all were negative. A rabbit inoculated with 1 cc. of an emulsion of the softened material into the ear vein remained well.

The appearance of the hardened brains corresponds very closely with that just described. Nowhere were any blood-vessels thrombosed or occluded in any way. Nowhere was there evidence of inflammation of the meninges. Section of the cerebral hemispheres showed irregular areas in the white matter of the occipital as well as the frontal lobes, and once in the temporal lobe, in which the brain substance had been softened and partly replaced by a translucent coagulated substance resembling agar. Shreds of greyish brain substance coursed through this clear gelatinous material. The adjacent greyish and opaque brain substance was studded with hæmorrhages through a thickness of about 3 mm. Where, as in some cases, the areas of softening were made up mainly of the greyish necrotic brain substance without much collection of fluid, the hæmorrhages were scattered throughout. In no instance did the cortical grey matter appear to be implicated, nor were the basal ganglia invaded.

Microscopically the lesions are practically identical in all the four cases except that while in all the process is quite acute, in one the destruction was less complete than in the others and the replacement of the necrotic material by coagulable fluid less extensive. A general view of a section carried through the cortex into the centre of such a focus shows the meninges practically normal, the elements of the grey cortex not notably altered, the nerve cells staining well, the blood-vessels patent and filled with blood. Passing inward the nervous elements begin rather abruptly to degenerate, disintegrate and disappear, and hæmorrhages begin to occur here and there; further toward the centre no more nerve cells are visible, axis cylinders are much degenerated, neuroglia cells stain badly, and the tissue has a much disintegrated appearance, being infiltrated with not very numerous polymorphonuclear leucocytes and fewer mononuclear round cells. Still further, and all evidences of tissue, except for small islands of necrotic substance, disappear in the highly refractive vacuolated hyaline material described (Plate VII, Fig. 1). We have then to consider in detail:

1. Changes in nervous elements.
2. Changes in neuroglia.
3. Changes in blood-vessels.
4. Changes in lymphatics.
5. Exuded fluid and cells.

The pyramidal ganglion cells which send down their axis cylinders through the degenerated area appear normal in the uninvolved portion of the cortex. The perigangliouic cells may perhaps be more than usually numerous. In the lower layers as one approaches the degenerated area the ganglion cells become swollen and granular, the nucleus stains less sharply, and the cell processes, so definite in the higher layers, have been lost or disappear after a very short course, forming mere projections from the outline of the cell. Many such cells take on a rounded outline and appear now as large, irregularly rounded, granular cells with rather diffusely staining nucleus. Indeed, as in Fig. 2 (Plate VII), such cells may be seen in the same field with their disintegrating processes which are slightly separated from the cell body; others still more degenerated have lost their nuclei. The much-degenerated cells lie in a tissue of axis cylinders and neuroglia which is thickly sprinkled with globules of various sizes of high refractive index and staining faintly bluish with hæmatoxylin. In specimens stained by Weigert's method these globules take the typical myelin stain.

The axis cylinders are somewhat swollen and thick and show evidences of disintegration (Plate VII, Fig. 3). They persist, however, fairly well into the completely necrotic substance, where they end abruptly. Throughout the degenerated area their myelin sheaths are broken up into the globules described above, many of which adhering to the axis cylinders give rise to the varicose appearances or bulbous swellings along the course of the fibril. In specimens prepared by Marchi's method such varicose beaded masses often stain black.

The neuroglia has also suffered severely. Traced by the aid of Mallory's special methods from the relatively normal cortex toward the centre of an area of softening, the dense matted feltwork of the outer region is seen to give place to a delicate network of finer deeply staining fibrils, which in their turn completely disappear further toward the centre, leaving the material there without any definite neuroglia stain and consisting of necrotic debris of cells and tissue without connecting supporting substance. Associated with this gradual disintegration of the neuroglia feltwork there are changes in the neuroglia cells. These lose the sharp contours of their nucleus, which comes to stain a diffuse greyish purple without any sharply stained chromatic particles; such nuclei become more and more indistinct and finally disintegrate.

Even more striking than these destructive degenerative changes in the nervous elements and the neuroglia cells and fibrils are the changes in the blood-vessels of the affected area.

It was stated above that examination of the vessels macroscopically and with scissors failed to reveal anywhere the presence of an occluding thrombus or embolus. Sections, too, made to pass through the blood-vessels in those brains already hardened when brought to the laboratory showed them to be filled only with blood. In the area of degeneration, however, wherever small vessels are left they may sometimes be found filled or partly filled with an elongated highly refractive hyaline mass, the free ends of which may be rounded off or pass over insensibly into the adjacent compressed and coalescing red blood-corpuscles. Such hyaline formations have been found mainly in the smallest vessels and in the degenerated area. Sometimes the lumen is only partly filled and the hyaline material may show gaps in which lie red corpuscles (Plate VIII, Fig. 5), or it may form a thick bluish-staining lining for the vessel in the lumen of which lie the red corpuscles.

The walls of the vessels in these areas show, however, extensive inflammatory changes. They are infiltrated (Plate VIII, Fig. 4) with cells of the type of the polymorphonuclear leucocyte for the most part, but occasionally mononuclear or so fragmented as to be difficult of diagnosis. This process affects arteries as well as the veins, and the infiltration extends throughout all the coats. The adventitial lymphatic sheath is in most cases distended and may contain masses of polynuclear and mononuclear cells with red corpuscles. Very often, however, this sheath contains only red corpuscles, but these in such numbers as to distend it to a diameter far greater than that of the blood-vessel. It seems most probable that this hæmorrhage has occurred by diapedesis, constituting one of the evidences of inflammation, but here and there there are apparently evidences of the direct rupture of the wall of a small vessel. The distended lymph sheath may also rupture; at any rate, in nearly every case there is a zone of hæmorrhage in the tissues round about it. Such extravasated red blood-corpuscles, like those within the sheath and the blood-vessel, are in a good state of preservation, indicating the extreme acuteness of the process. There is nowhere any definite accumulation of hæmatoidin or hæmosiderin to be found in the tissues or in the lymphatics—further evidence of the rapid course of the disease.

The small vessels lying in the centre of such hæmorrhages are very commonly such as are plugged with the rather blue-staining hyaline masses already described (Plate VIII, Fig. 5). Other vessels may contain a similar hyaline material and indeed hyaline is often found both within and surrounding the vessel. Especially is this true in the case of some of the larger vessels lying within those meningeal processes

which pass deep into the sulci. There the surrounding tissue is spread apart by the presence of this coagulated material.

The nature of the hyaline substance offers perhaps some difficulty of explanation. Leyden and Goldscheider[1] express themselves as follows:

> Sometimes in œdema, softening or acute inflammation of the cord one finds in sections structureless amorphous masses. These occur in the central canal, in the grey substance, less often in the white matter, often about the vessels. This phenomenon is explained in various ways: by some thought to be coagulated albuminous or fibrinous exudate, by others interpreted as a colloid, hyaline, mucoid or gelatinous degeneration of softened nerve substance or swollen and diseased neuroglia. It is this structureless mass which Lockhart Clarke described as "granular or fluid disintegration." According to that author it consists in a softening and destruction of the nerve tissue and its change into a granular mass which, with the exuded fluid, mixes to form a homogeneous substance. These masses take the carmine stain very weakly. Their nature is not yet settled; it is even questionable whether the material under discussion is everywhere the same. The perivascular masses are most probably exudate; whether this will hold for all similar forms is, however, uncertain. The attempts to determine the nature of the substances by various stains have so far not been successful.

The problem before us is somewhat similar. The hyaline material within and about the meningeal vessels looks at times as if it had been produced by the coalescence of red corpuscles, but in general it is too abundant and homogeneous to be so explained. It is rather denser and more refractive than coagulated plasma would appear, and with water blue it stains brilliantly. In its general appearance and reaction it agrees fairly well with the larger hyaline masses in the areas of necrosis. Such hyaline material occurs also scattered about among the tissue elements, but nearly always about a vessel except in the most degenerated areas where the tissue becomes necrotic and entirely gives place to the structureless mass. There is even difficulty at times in outlining this necrotic substance from the hyaline material. Highly refractive as elsewhere it shows here, too, the tendency to contract and leave vacuoles, probably as the effect of the hardening reagent, so that the great central mass has, as a rule, an appearance almost like the cut surface of a Gruyère cheese (Plate VIII, Fig. 6). Often in such vacuoles a delicate coagulum can be made out, suggesting the presence there of a fluid of less density. The highly refractive substance is somewhat denser about the vacuoles. It is apparently very brittle in

[1] Die Erkrankungen des Rückenmarks und der Medulla oblongata, in Nothnagel's Spec. Path. u. Therap., Bd. X, Wien, 1897.

the sections and shows cracks and fissures here and there. It stains with eosin, taking a fairly bright pink color; Congo red tinges it brick red. Van Gieson's stain leaves it pinkish yellow—neither definitely red nor definitely yellow—with water blue and fuchsin it stands out sharply from the adjacent substance by its bright deep blue color; so also do the masses in and about the vessels. With Mallory's phosphotungstic acid hæmatoxylin it stains a rather pale purplish pink; with his modified stain for connective tissue as applied to the nervous system, it takes a dense deep purple color. With methylene blue, carbol fuchsin, Weigert's fibrin stain, etc., it is hardly tinged at all. Osmic acid does not stain it; in a Marchi preparation it is just visible as a smoky area.

The material stains therefore with acid dyes, in which respect (according to the hypothesis of P. Ernst) it corresponds to that form of hyaline derived from epithelial cells. Nervous elements being of epiblastic origin, might perhaps furnish the great mass of hyaline in the centre of the focus. There would be difficulty, however, in thus explaining the presence of a substance staining in exactly the same way in and about the arteries as well as the veins, and we must probably consider this one of the exceptions to the rule, as is the colloid of the thyroid which, although derived from epithelium, stains red with Van Gieson's stain.

In the smaller vessels in the neighborhood of the most intense degenerations the hyaline masses described above stain rather bluish with the hæmatoxylin and eosin stain, which seems to indicate that they are not quite identical in nature with the remaining hyaline substances described.

As stated above, the central hyaline mass in each focus is bounded by ragged edges of necrotic substance with here and there free islands of such tissue. Nowhere are there any evidences of the least pressure on this tissue, which becomes gradually rarefied toward the margin, where it quite disappears. This mass is, therefore, in all probability the result of the breaking down of the brain substance—perhaps added to also by exudation of fluid from the vessels.

The exudation of leucocytes is not very abundant in the sections. Beside the infiltration of the walls of the small vessels and the tissue surrounding them, leucocytes are found sprinkled in considerable numbers through the most degenerated tissue in the focus where it borders upon the hyaline material. These leucocytes are easily distinguished by their sharp staining from the greyish purple degenerated neuroglia nuclei which persist there.

Besides the leucocytes there are a few somewhat larger round cells with small single round nucleus and granular protoplasm. These appear to be analogous to the fat granule cells which are so common in inflammatory diseases of the nervous system of longer standing, they are however rather scarce, and although in a Marchi preparation they can be made out to contain blackened fat droplets, they are by no means a prominent feature in the section.

The process is therefore predominantly a destructive rather than an exudative one. To resume, we have an acute disease, rapidly fatal, producing large areas of complete destruction of the brain substance in which the anatomical elements are disintegrated and largely replaced by a colloid-like material. In the neighborhood the blood-vessels are acutely inflamed, there is exudation of leucocytes into the vessel walls, and throughout the adjacent tissue, with passage of the red corpuscles into the perivascular lymph sheath and into the adjacent tissues, these focal extravasations giving the inflammatory process its hæmorrhagic character.

The various forms of acute hæmorrhagic encephalitis in man as described by Wernicke, Strümpell, Friedmann and others seem, as a rule, to progress less rapidly and to be much less violently destructive than this form. Anatomically, however, the conditions are analogous.

In horses the disease is apparently fairly well recognized. Friedberger and Fröhner,[2] giving the bibliography, summarize the results of investigation into the pathology of acute encephalitis about as follows:

> Local non-purulent encephalitis occurs in irregular, round foci, mostly of the size of a pea to that of a hen's egg, sometimes even involving a whole lobe of the brain, but not sharply limited. At first the place is slightly diffusely reddened, this being soon followed by a swelling and softening from serous exudation, when, according to Schütz, the cells of the neuroglia and the ganglion cells are swollen and granular, and finally undergo fatty degeneration; the axis cylinders are varicose and the glia tissue infiltrated with small cells. The focus undergoes maceration, swelling and liquefaction, resulting finally in a softened mass consisting of disintegrated and fatty glia and ganglion cells, leucocytes and free fat-globular cells, and is spoken of as simple inflammation of the brain or inflammatory softening of the brain, distinguishable from ischæmic

[2] Lehrb. d. spec. Path. u. Therap. d. Hausthiere, Bd. ii, p. 79, 2te Aufl., Stuttgart, 1889.

encephalomalacia by the exudation of leucocytes. This may be all, but often there are complicating hæmorrhages giving rise to hæmorrhagic inflammation of the brain. With the decomposition of the hæmoglobin in such a focus the color disappears gradually and becomes yellowish. Then, as the mass of disintegrated tissue and exudate becomes more fluid, there is formed either a grey gelatinous mass or cyst, or finally a scar arises.

This description would apply to the cases described above fairly well except that the gelatinous fluid mass appears only at the end where the process is on the way to healing, whereas in our cases the brain substance throughout a large focus is quickly reduced to a gelatinous, structureless mass of necrotic and hyaline material.

The single case of our series in which recovery from the disease had occurred showed in the frontal lobe of one hemisphere a depression which on section of the brain corresponded with an elongated, grey, translucent scar which ran deep into the substance of the brain. This microscopically showed only a loose granulation tissue with numerous cells resembling the fat granule cells. Of course, whether or not it was really the end product of such a condition as described above depends on the accuracy of the diagnosis, but as the symptoms are fairly characteristic and the scarred condition of the brain about what might be expected as the final result of the anatomical process, it seems probable that this was an instance of recovery from the affection here described.

Addendum.—Since the above was sent to press there has occurred another outbreak of the disease in southern Maryland in the course of which great numbers of horses have died. We were able to make three autopsies on animals in which the symptoms during life were such as are described above. The two horses when seen were comatose while the third animal—a mule—had died after a short but violent delirium. As the horses were obviously dying they were killed, but the autopsies revealed no recognizable macroscopic lesion. Microscopically, however, the vessels in the substance of the brain show in many places an acute inflammatory affection of and around their walls, and here and there in their neighborhood there is infiltration of the tissue with mononuclear, polymorphonuclear and eosinophilic leucocytes. No widespread destruction such as that described for the previous cases was found in these cases, and it is clear that they represent an earlier stage of the affection than that described above.

Bacteriological examination in these cases led also to no satisfactory results. Cultures from the organs of the horses were sterile except for occasional obvious contaminations. A rabbit inoculated with an emulsion of the brain substance of the mule, which had been dead 48 hours, died with a general infection with a bacillus probably of the hog-cholera group and very virulent to rabbits. Further study of this organism will be made but it is not likely that it has any relation to the disease in question.

DESCRIPTION OF PLATES VII AND VIII.

PLATE VII.

Fig. 1. Photograph of a section through part of a focus of encephalitis showing the disintegration of the white matter, and the central hyaline substance.

Fig. 2. Ganglion cells which are losing their processes and becoming rounded—steps toward their complete disintegration.

Fig. 3. Nerve fibres undergoing degeneration. The myelin sheath forms droplets or varicosities along the axis cylinder. Other highly refractive droplets are scattered about in the tissue.

PLATE VIII.

Fig. 4. Small vessel with cellular infiltration of the wall, the perivascular lymph sheath being distended with blood.

Fig. 5. Similar vessel with extravasation of blood into its lymph sheath. The vessel is partly filled with a hyaline material.

Fig. 6. Central portion of a large focus showing the margin of the necrotic material and the central hyaline substance with vacuoles.

FIG. 1.

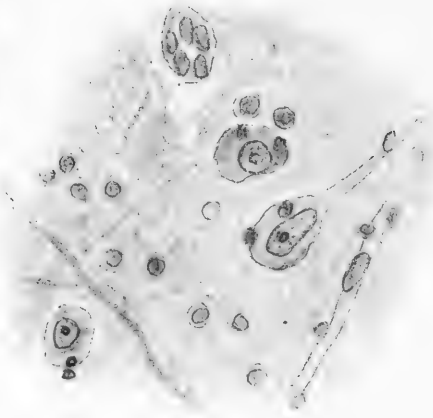

FIG. 2.

FIG. 3.

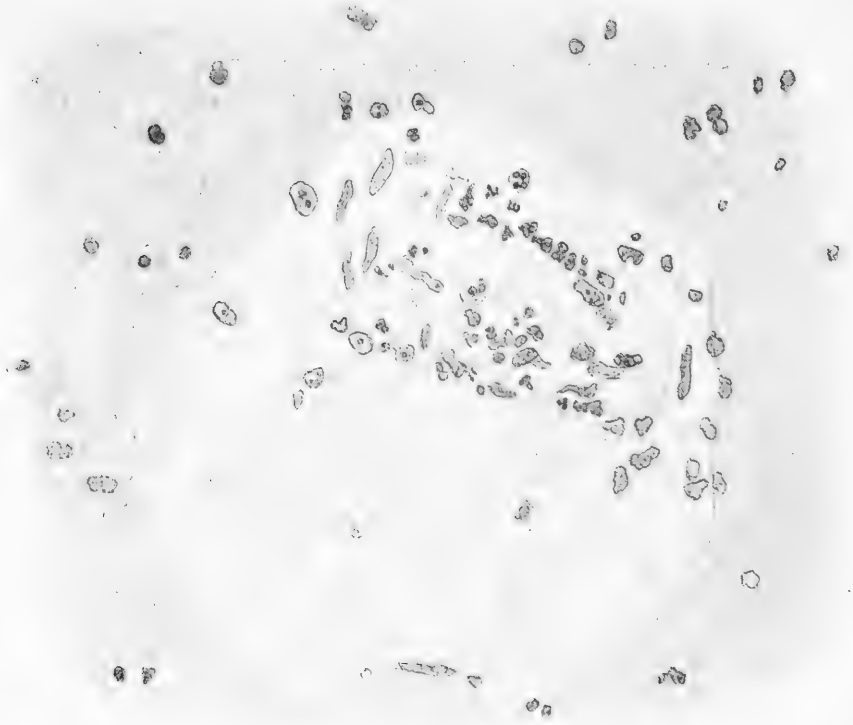

FIG. 4.

FIG. 5.

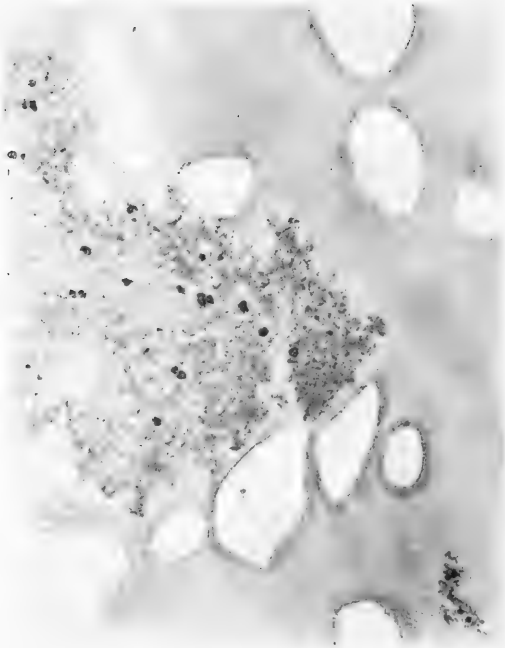

FIG. 6.

ON THE OCCURRENCE OF STRONGYLOIDES INTESTINALIS IN THE UNITED STATES.

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PLATE IX.

HISTORICAL.

In 1876 Normand (1876),* a French naval surgeon, discovered a small nematode in the dejecta of patients who had contracted severe diarrhœa in Cochin China. This parasite, present in enormous numbers, was afterwards studied more carefully by Bavay (1876), who described it as *Anguillula stercoralis*. The worm, according to Bavay, differs but little from the terrestrial anguillula, *Rhabditis terricola* Dujardin, genus *Leptodera* of Schneider. The parasites were usually met with, in the stools, as larvæ, measuring about 0.33 x 0.022 mm. in size. When the stools were kept in uncovered vessels at a sufficiently warm temperature, these larvæ underwent development, reaching full growth and sexual differentiation in about five days. The length of the full grown female was about 1 mm.; its breadth about 0.04. The body was cylindrical, slightly diminishing in size anteriorly and tapering to a sharp point posteriorly. When the worm retracted forcibly, slight transverse furrows were to be seen. The mouth as described by Bavay, possessed three distinct lips, and was continuous with the triangular œsophagus, which, after a stricture, dilated again into a second ovoid enlargement. The intestine, which followed, was fairly visible, and ended in a little protrusion on one side of the body near the base of the tail. The intestine was pushed slightly aside by the uterus. A little below the middle of the body, and on the ventral side, opened the vulva, leading to the uterus, which extended from the intestinal ventricle to a point near the anus. Here the eggs were massed in varying number. In some instances the young had actually broken the shell of the eggs, and were free in the uterus, though more often the eggs, on deposition, contained well formed, motile embryos.

* References to authors are arranged alphabetically at the end of this article.

The male was about one-fifth smaller than the female. The peri-intestinal cells were more clearly outlined, and were accompanied by another long gland, which seemed to consist of small rounded globules. This organ, doubtless the testicle, ended at the base of the tail in two small, horn-like spicules with tapering extremities curved inward; these spicules contained canals. They were of equal length, and were situated symmetrically on a transverse plane. The tail, which was coiled also in the same direction as the spicules, was twice as short as that of the female. The authors further described copulation, the laying of eggs and the development of larvæ. Neither Normand nor Bavay were able to cultivate the adult animal from the second generation.

In the following year Normand (1877) discovered a second nematode, present, in association with these parasites, in the small intestine of a patient dying from Cochin China diarrhœa. Bavay (1877 [1, 2]), who afterwards found this parasite in a number of autopsies upon similar cases, described it as a distinct species, which he termed *Anguillula intestinalis*. It was met with only in the female form, the length of which was 2.20 mm.; the average breadth 0.03. The body, a little tapering anteriorly, terminated, rather suddenly, posteriorly in a conical tail, the extremity of which was appreciably rounded, and even a trifle dilated. With a sufficient magnification, the surface showed a very delicate transverse striation. The mouth, without horny armature, showed three small lips. It opened into an œsophagus, practically cylindrical, which occupied about one-fourth of the length of the animal, and showed neither swellings nor striations. It was followed by an intestine, with which one might readily confound it, without a marked change of color. This intestine extended nearly to the posterior extremity of the body, but it almost ceased to be visible in the middle part, which was occupied by a very large, elongated ovary. The vulva was situated in the posterior third of the animal, and, in its neighborhood, the uterus contained usually five or six rather elongated eggs. The anus, a transverse slit, was situated toward the base of the tail. The eggs and the viscera were of a yellowish green color, rather opaque and apparently finely granular. All individuals observed were oviparous females. Bavay questioned whether the absence of males was due to their prompt disappearance after coupling, or whether, as Schneider has shown to be the case in certain nematodes, the worm is unisexual when free, and hermaphroditic with a female habitus when parasitic.

These worms were abundant in the duodenum, rarer in the jejunum;

they were not found as far down as the ileum. Once, they were found in considerable numbers with embryos of *A. stercoralis* in fluid coming from the stomach. In intestines where the worm was found, it was not uncommon to find also series of eggs, often joined together, sometimes isolated. In some of these the embryo, in the process of formation, showed a definite row of dorsal cells; in others its development was more advanced.

These parasites were hardly ever found in the stools. Bavay (1877 [2]) found the worm in six cases, and in five of these only at autopsy. The development of the eggs was not observed, but Bavay (1877 [2]) makes the following statement:

"In three diarrhœic stools which we had preserved to follow the development of the *Anguillula stercoralis*, we found, at the end of several days, that they contained larvæ different from the first. These were, as a matter of fact, longer, with a cylindrical œsophagus descending down to about the middle of the body, and a tail, which, instead of terminating in a fine point, was, on the contrary, apparently truncated at its extremity. Although the culture of these larvæ could not be carried far enough to establish in an irrefutable fashion their identity with the *Anguillula intestinalis*, yet we had no doubt with regard to this point. Indeed, two of the patients who presented this form in their stools, have succumbed since then, and the autopsy has shown us the complete form. The third case still lives."

Both Normand and Bavay were inclined to regard the parasites, especially *Anguillula stercoralis*, as important etiological factors in Cochin China diarrhœa.

These observations were partly confirmed in 1877 and 1878 by Laveran (1877 [1, 2]), Libermann (1877 [1, 2]), Roux (1877) and Chastang (1878) in patients from China, and by Chauvin (1878) in a case originating in Martinique. Their observations related almost entirely to the discovery of rhabditiform embryos in the stools. Chauvin, however, states that he was able, in cultures, to follow the deposition of the eggs by the adult female, and that he noted the presence, together with the embryos of the new generation, of a longer, thinner and more motile worm, "probably that which has been mentioned by Normand."*

In 1878 Grassi (1878, 1879 [1, 2]) and Parona (1879) discovered *A. intestinalis* at a number of autopsies in Pavia, and published a careful description of the mother worm, of the eggs and of the embryos developing from them.

The mother worm was found throughout the upper gastro-intestinal tract, especially in the lower part of the duodenum and the upper

* Normand (1877) quotes Bavay (1877 [2]); vide supra.

part of the jejunum, though they were occasionally met with throughout the jejunum and in the upper part of the ileum. They have been found in the stomach. In some cases the intestinal mucosa appeared to be perfectly healthy. The eggs, deposited in the intestinal tract, hatched almost immediately after being laid. They were found, as a rule, in close proximity to the mother worm. It was extremely rare to find the eggs in the stools. The embryos in the fæces, which were almost exactly similar to those described by Normand and Bavay as *A. stercoralis*, were identical with those found in the intestine. In cultures kept at room temperature in July, the fæces being moistened with a little water, these worms were found to grow gradually, until, after four or five days, sometimes longer, they measured about 0.6, while the breadth diminished to about 0.015. The two bulbous enlargements disappeared from the œsophagus, which occupied more than a third of the entire length of the animal, and was bordered by granulations. The genital rudiment had disappeared. After ten or twelve days, many of the worms were 0.75 long, but the longest were only about 0.029 or 0.03 in width; the œsophagus occupied one-half the length of the animal.

It was pointed out that, at this stage, the embryos were similar to those forms observed by Bavay and Chauvin in fæces which had been kept for some time; forms which Bavay (1872 [2]) had believed to be larvæ of *A. intestinalis*.

They failed to observe in their cultures, at autopsy, or in the stools, a single sexually differentiated *A. stercoralis*.

Grassi (1879 [1]) placed the worm in a special genus, closely allied to *Strongylus*, which he termed *Strongyloides*, and later (1879 [2]) he suggests the specific term *Strongyloides intestinalis*. This classification has been accepted by the best authorities.

At the same time Perroncito (1880 [1-6], 1881, 1882, 1883) called attention to the presence of *Anchylostoma duodenale* and also *Anguillula intestinalis* and *A. stercoralis* in the intestinal tract of workers in the St. Gothard tunnel. He (1881, 1882) succeeding in cultivating, from rhabditiform embryos found in the fresh fæces, adult *Anguillula stercoralis*, which he termed *Pseudo-rhabditis stercoralis* (Bavay). The original rhabditiform embryos were, from his descriptions, essentially similar to those described by Normand, Bavay, Grassi and Parona. He described and pictured with accuracy the development of the adult male and female forms from the rhabditiform embryos in the stools, their copulation, the laying of eggs, the hatching of these, and the gradual transition of the young embryos of the second generation into filariform larvæ,

very closely similar to those described by Grassi and Parona as the final stage of the metamorphosis of the rhabditiform embryos, the descent of which from *Anguillula intestinalis* they had traced.

Perroncito also described *A. intestinalis*, but contrary to the observations of Grassi and Parona, he asserted that the eggs of this worm appeared in great numbers in the stools, and were, at some stages, indistinguishable from those of *Anchylostoma duodenale*. In cultures, the larvæ developing from these eggs were closely similar to those of *Anchylostoma*, the differences described being extremely slight.

The differences between the larvæ of *Anguillula intestinalis* and *A. stercoralis*, Perroncito believed to be slight but yet characteristic. He maintained, however, that the larvæ of *A. intestinalis* and *Anchylostoma* were never found in recent fæces. In his own words: "This is sufficient of itself to establish the diagnosis" (1880 [3]).

These observations were followed by a rather spirited controversy, Grassi (1882, 1883 [1, 2, 3]) maintaining, and proving beyond a doubt, that Perroncito had fallen into error in assuming that the eggs of *A. intestinalis* were passed in any number in the fæces. He showed, clearly, that Perroncito had been dealing purely with *Anchylostoma* eggs. He insisted that the rhabditiform embryos found in the dejecta were direct descendants of the strongyloid so-called *Anguillula intestinalis*, and, in view of the apparently clear evidence that these embryos often develop, in cultures in the free state, into sexually differentiated adult parasites, so-called *Anguillula stercoralis*, he advanced, in 1882, the hypothesis, based upon a number of observations, that *Anguillula intestinalis* was a dimorphobiotic parasite like *Ascaris nigrovenosa*; that the mother worm in the intestine was parthenogenetic or hermaphroditic; that the rhabditiform embryos developing from the eggs of these and escaping in the dejecta, developed into a sexually differentiated generation outside of the body; that the descendants of this sex-ripe generation were capable, after ingestion, of developing again, into the parthenogenetic or hermaphroditic parasitic mother worm.

In the same year there occurred, in the clinic of Gerhardt at Würzburg, a case which was carefully studied by Seifert (1883 [1, 2]), Grassi, and Leuckart (1883), which was destined to shed much light upon this disputed question. Seifert sent specimens of the dejecta to Leuckart in Leipzig. These contained great numbers of typical rhabditiform embryos, unquestionably similar to those described by Normand, Bavay, Perroncito on the one hand, and by Grassi and Parona on the other. In cultures, these developed into sexually differentiated *Anguillula stercoralis*. The new embryos developing from the eggs of these under-

went the course of development described by Normand, Bavay and Perroncito, changing, eventually, into characteristic filariform larvæ. Leuckart was convinced that these filariform larvæ must pass over into a suitable host to return to complete development and sexual maturity, and from analogy with what he had previously observed in *Ascaris nigrovenosa*, he agreed with Grassi in assuming that these various forms were but different phases in the cycle of a single heterogenic parasite. "The structure of the filariform larvæ is such that they cannot possibly develop again into the rhabditis form. There must be another worm which develops from them, a variety which, in the shape of its body and the structure of the œsophagus resembles these." And *Anguillula intestinalis* possesses these characters. Owing to the entire absence of males he believed, as did Grassi, that the parasitic mother worm, of female habitus, was hermaphroditic or parthenogenetic. While he expressed no positive opinion, he was inclined to suspect that, as Schneider had shown to be the case in the analogous stage of *Ascaris nigrovenosa*, the so-called *Anguillula intestinalis* was hermaphroditic.

More recently, however, Rovelli (1888), who has investigated this question, has come to the conclusion that the worm is parthenogenetic.

Leuckart was strengthened in his views concerning the life history of the parasites by the fact that Grassi and Parona (1879) had demonstrated the origin of the rhabditiform embryos found in the dejecta from *A. intestinalis*, while both Bavay and Grassi (also Chauvin (1878)) had described filariform larvæ in old cultures. He suggested for the parasite the name *Rhabdonema strongyloides*, and in conclusion says: "The *Rhabditis stercoralis* itself is to be erased from the list of essential parasites; it represents, like the *Rhabditis ascaridis nigrovenosa*, despite its sexual differentiation, an intermediate generation, developing externally, which forms a link in the chain of development of the *Anguillula intestinalis*."

At the suggestion of Grassi, who also observed this case, the patient was given on several occasions large doses of male fern, santonin and thymol. On one occasion, after an anthelmintic followed by a purge, two examples of the mother worm were recognized by Grassi (Seifert, 1883 [2]) in the fæces; both, however, were dead and had undergone considerable post-mortem change. On another occasion, after administration of apomorphia, a considerably degenerated *A. intestinalis* was found in the vomitus. No examples of sexually differentiated adult *A. stercoralis* were ever observed in the fresh stools.

In the same year Grassi (1883 [1]) emphasized the interesting fact that filariform larvæ, identical with those into which the primarily rhabditi-

form embryos of the free living generation develop, may arise by *direct* transformation from the rhabditiform embryos of the parasitic mother worm, namely, the embryos found ordinarily in the dejecta. This direct transformation had been clearly described by Grassi and Parona (1879) four years before, and in the experience of the former, represents the ordinary method of development.

In support of these observations showing that the rhabditiform embryos of the parasitic mother worm may, under some circumstances, change directly into the filariform larvæ, without the interposition of the sexually differentiated free living generation, Grassi (1883 [1]) notes the fact that exacerbations of the infection in patients who have been living in regions where fresh infection by the mouth is out of the question, are not uncommon. He also points out that it is not infrequent to find, in the cadavers of individuals who have remained in hospitals for several months, small and rather immature examples of *A. intestinalis*. Such a parasite was passed by the Würzburg patient. There is no evidence that the sex-ripe intermediate generation ever develops in the intestinal tract during life. Such forms are never found at autopsy. The presence, then, of immature forms of *A. intestinalis* at autopsy, and the increase in the number of embryos in the stools during life, must depend upon a direct transformation of the rhabditiform embryos into the mother worm without the interpolation of the sexually differentiated generation.

In 1884, Golgi and Monti (1884, 1885) made a careful study of this question in cases observed in Pavia. They confirmed *in toto* the observations of Grassi and Parona, and agreed with these observers in pointing out Perroncito's error in assuming that the sexually differentiated, free living generation is a separate parasite. They followed in cultures the direct transformation of the rhabditiform embryos of the parasitic mother worm into the filariform larvæ, as well as the indirect change through the free living, sexually differentiated generation. They agreed with Grassi in believing the former cycle to be the commoner.

In the meantime a number of other observers had described cases in which this worm was present: Breton (1879) in China; Sahli (1882) and Bozzolo and Pagliani (1880) in cases from the St. Gothard Tunnel, Ribeiro da Luz (1880) and Lutz (1885) in Brazil; Radetski (1886) in Russia; while Grassi (1878), Grassi and Calandruccio (1884), Grassi and Segrè (1887), Lutz (1885), and others described similar parasites in other animals. Since then Calandruccio (1889 [1, 2]) and Barbagallo (1897) have found the parasite in Sicily; Sonsino (1889, 1891), Riva (1891) and de Silvestri (1895) in Italy; Ilberg (1892) in a case from the

Dutch Indies; Sonsino (1896) in Egypt; while Leichtenstern (1898, 1899) and Wilms (1897) have described a number of cases occurring especially in brickworkers along the Rhine, and Poppenheim (1899), a sporadic case in East Prussia. Pérez Valdés (1897) has observed the parasite in Spain, and Strong (1901) in the Philippine Islands.

The most important work of recent years has been done in the clinic of Leichtenstern. As a result of fourteen years' study of fourteen cases, this observer comes to the following conclusions (1898):

"(1) The direct metamorphosis of the Anguillula embryos into the filariform is the rule. In some of my patients with Anguillula, this method of development was observed exclusively for weeks and months, however one might vary the conditions under which the cultures were made.

"(2) The development of the sex-ripe intermediate generation, *Rhabditis stercoralis*, takes place commonly, but by far not so constantly and regularly as the direct metamorphosis.

"(3) In those cases again, which, in my experience, are unusual, where the development of the sex-ripe intermediate generation predominated continually or for transient periods, I have never failed to observe the direct metamorphosis as well.

"It is then a matter of purely facultative, by no means exclusive or obligatory heterogenicity."

As to the reason why, in one instance, the direct method of transformation should prevail, and in another the indirect, there has been much question. Wilms (1897), in Leichtenstern's laboratory, has proved definitely that it is not due to the existence of two distinct varieties of worm. This observer administered to human beings filariform larvæ which had developed by the method of direct transformation from rhabditiform embryos of the parasitic mother worm. After seventeen days, rhabditiform embryos began to appear in the patient's stools. In culture experiments these characteristic rhabditiform embryos underwent, in part, a direct metamorphosis into new filariform larvæ, but in part, developed into the sexually differentiated, free living generation, the so-called *Rhabditis stercoralis*, from the eggs of which, in turn, there arose rhabditiform embryos changing rapidly into filariform larvæ.

Experiments with culture media, variations in the temperature, moisture, etc., to which the cultures are exposed, have failed to reveal any definite law as to the reason for the prevalence of one or another of these methods of development. Leichtenstern (1899), in his last article, has pointed out the fact that the sex-ripe intermediate genera-

tion is apparently commonest in cases which have been but recently imported from the tropics, while the direct metamorphosis is the rule among those instances originating in Italy, Belgium, Germany and Holland. It is, however, probable that all these worms were ultimately of tropical origin. So that one may be led to believe that the parasite, after entering into temperate regions, has adapted itself to the less favorable climatic outward conditions, in that in temperature zones, it tends to follow the direct method of transformation into the filariform larvæ, a method which is simpler, more rapid and less dependent upon outward influences. And yet, despite this, in any given case there may, for a certain time, occur a change, as a result of which the development of the sexually differentiated intermediate generation prevails. The cause of such variations in the type of the cycle of development is quite obscure.

The only observer of recent years who has failed to recognize the heterogenicity of the parasite is Teissier (1895 [1, 2]), who in 1895 reported a remarkable instance in which the stools contained worms which he believed to be identical with the rhabditiform embryos above described. In cultures they developed into sexually differentiated free living parasites closely similar to those described by Bavay, Perroncito, Grassi and others. In the circulating blood, however, there were also found numerous small larvæ which he believed to be the earliest stages of these embryos. Contrary to the experience of almost all other observers, Teissier found adult, sexually differentiated forms, not only in cultures, but also in the fresh dejecta, and concludes that *Anguillula stercoralis* is a separate and distinct parasite.

There are, however, certain points in which his observations vary materially from those of others. In the embryos found in the blood, and the smallest forms observed in the fæces, which were from 220 μ in length, by 10-12 μ in breadth, no internal structure could be made out. All recent observers, however, have noted that excepting perhaps, in the very earliest stages, the embryos developing from the eggs of both parasitic and free-living generations, show, already, the characteristic double œsophageal enlargement. Teissier's description of the adult parasite also varies from those given by Normand, Bavay, Grassi, Perroncito and others, in that he was able to distinguish but one spicule in the male, instead of two, as noted by all other authors. The character of the young larvæ, the presence of adult forms in the fresh dejecta, the slight differences in the structure of the male parasite, might give rise to the suspicion that Teissier may have been dealing with a different species of a closely allied parasite.

In a later article Teissier describes remarkable results obtained by inoculating these parasites into frogs—results which, if confirmed, would support this idea. After inoculation he believed that the worms developed in the intestinal tract and lungs of the frog, into giant forms. It is not impossible that these giant forms may have been *Ascaris nigrovenosa* [= *Rhabdonema nigrovenosum*].

It should be remembered, however, that Teissier is not the only observer who has recognized what he believed to be adult forms of *Anguillula stercoralis* in the fresh dejecta. Normand (1877) stated that he had met with all known forms of the worm at autopsy. In 1878 he asserted that "nothing is rarer than to see *Anguillula stercoralis* in a state of complete development in dejecta of recent origin"—a statement which would justify the inference that he had seen such forms. In this latter article he also expresses his positive opinion that the adult forms do develop in the gastro-intestinal tract.

In consideration of the fact that these views are at variance with those of most other observers, and of the somewhat indefinite character of Normand's statements, it has been assumed (Leuckart, 1883) that the sexually differentiated *A. stercoralis* may develop in the intestine, but only after death when the conditions are essentially the same as in cultures outside of the body, a theory which would account for one of Normand's statements. It must be acknowledged, however, that this does not cover his apparent assertion that he had met with adult forms in fresh dejecta.

In view of the statements of these two observers, it would, perhaps, at the present time, be unwise to deny the possibility that, in rare instances, the sexually differentiated intermediate generation may develop within the human host.

CLASSIFICATION.

The following classification has been generally adopted:

Family: *Angiostomidae.*
Genus: *Strongyloides* Grassi, 1879.
Syn.: *Pseudo-rhabditis* Perroncito, 1881.
Rhabdonema Leuckart, 1882, pro parte.
Species: *Strongyloides intestinalis* (Bavay, 1877).
Syn.: *Anguillula stercoralis* (Bavay, 1877).
Rhabditis stercoralis (Bavay, 1877).
A. intestinalis (Bavay, 1877).
Leptodera stercoralis (Bavay, 1877) Cobbold, 1879.
Leptodera intestinalis (Bavay, 1877) Cobbold, 1879.

Strongyloides intestinalis (Bavay, 1877) Grassi, 1879.
Pseudo-rhabditis stercoralis (Bavay, 1877) Perroncito, 1881.
Rhabdonema strongyloides Leuckart, 1883.
Rhabdonema intestinale (Bavay, 1877) R. Blanchard, 1885.

It may perhaps be well to emphasize one point in connection with the synonymy. Most of the recent text-books—Railliet (1895), Moniez (1896), Braun (1895), Weichselbaum (1898)—in their synonymy, refer to the special term *Strongyloides intestinalis* as having been introduced by Grassi in 1883. I have searched the literature with considerable care, but have been unable to find any reference to the worm under this name in Grassi's publications of that year. The name, however, was first used by Grassi four years before. In an article in the *Rendic. r. Ist. lomb.*, Milano, 1879, xii, ser. 2, p. 228, he proposes the generic name *Strongyloides*, and in a review of his own article, in *La med. contemp.*, Milano, 1879, iii, 495, he says: "He concludes by referring *Anguillula* to a new genus, *Strongyloides*, which" (*Anguillula*) "should therefore be called *Strongyloides intestinalis*." I have been unable to find any reference to this name in later publications by Grassi. In his articles appearing in 1883, he apparently accepted the classification of Leuckart—*Rhabdonema strongyloides*.

PATHOLOGICAL SIGNIFICANCE.

The fact that the worms were so frequently present in the severe diarrhœas of Cochin China led Normand (1876, 1877, 1878) to assume that they played an important part in the ætiology of the disease. At that time, of course, the so-called *Anguillula intestinalis* and *Anguillula stercoralis* were regarded as distinct species. Normand (1877) recognized the fact that the parasites may exist in the intestinal tract for considerable periods of time without producing any serious symptoms. Man may harbor the worm for years with little or no inconvenience; there may be noted, perhaps, only a slight softness of the dejecta, or occasional transient attacks of diarrhœa. Anything, however, which tends to diminish the resistance may offer to the worms the opportunity to produce those intestinal changes which result in the clinical picture of Cochin China diarrhœa. This view was upheld by Laveran (1877 [1, 2]), Davaine (1877), Dounon (1879), Roux (1877) and Ribeiro da Luz (1880). Libermann (1877 [1, 2]), however, was very reserved in his views as to the part played by the worm.

On the other hand, Chastang (1878), Breton (1879), Lutz (1885) and Calmette (1893) were inclined to doubt its pathogenicity. Grassi (1879 [1]) found the parasites in the stools of many healthy individuals

and while confessing that it was hard to believe that their action was not in some way harmful, yet he had never been able to make out any special symptoms attributable to the infection. He did not believe that the parasite was the cause of Cochin China diarrhœa. Later (1883 [2]) he asserts positively that "Anguillulæ are innocent commensals of man."

Golgi and Monti (1884, 1885), however, found distinct anatomical changes which they believed to be dependent upon the irritative influence of the worms, evidences such as could leave no doubt that, in some cases at least, the parasites must have a pathological significance, while Sonsino (1891) in a study of two fatal cases found evidence that the embryos may actually penetrate into the mucosa. He, as well as Golgi and Monti, frequently found worms occupying the lumina of Lieberkühn's ducts, while later, in the same cases, Venturi (Sonsino (1891)) discovered eggs and embryos in the depths of the villi and mucosa. Sonsino is strongly of the opinion that the worm may cause serious and even fatal changes. Riva (1891) likewise, from the study of a fatal case, is convinced of the pathogenic importance of the parasite, which he is inclined to consider the essential causal agent of the disease. The action of the worms is, he believes, wholly mechanical. More recently, Askanazy (1900) also has demonstrated that the worms may actually penetrate into the submucosa.

Teissier (1895 [1, 2]), indeed, has reported a remarkable instance in which small filariform larvæ were found in the circulating blood, worms corresponding closely to the larvæ of a parasite present in the stools, and identified by him as *Anguillula stercoralis*. As has been mentioned, however, there were peculiarities about the case observed by Teissier which are sufficient to give rise to some doubt as to the identity of the larvæ present in the blood.

Leichtenstern (1898), who has observed the constant presence, through years, of great numbers of the rhabditiform embryos in the stools of individuals in a relatively normal condition, while recognizing the fact that the presence of such enormous numbers of parasites may have a marked effect in increasing the severity of a diarrhœa when present, yet feels convinced that such a diarrhœa must owe its origin to some other primary cause, a view similar to that previously expressed by Calmette (1893).

Perroncito's (1880 [1, 2, 3, 6]) theory that the parasite played an equal part with *Uncinaria duodenalis* in the production of the severe anæmias observed in miners and tunnel workers, has long since been disproven. The removal of *Uncinaria* by proper treatment is sufficient to dispel

all symptoms of miners' disease, despite the fact that great numbers of the rhabditiform embryos of *Strongyloides intestinalis* frequently persist in the dejecta for long periods of time after the disappearance of all evidence of the sister worms.

The weight of evidence appears to be in favor of the view that, while the parasites may exist in the intestine for long periods of time without ill effects, they are by no means, as Grassi says, "innocent commensals of man." It would seem probable that this parasite alone may be the primary agent in many cases of chronic diarrhœa.

The deleterious influence of the worm is generally supposed to be purely mechanical [Golgi and Monti (1884, 1885), Sonsino (1891), Riva (1891), Askanazy (1900)], although Calmette (1893) suspects that the parasite may give rise to substances acting as chemical irritants.

CLINICAL MANIFESTATIONS.

The clinical picture described by Normand (1877) in his cases of Cochin China diarrhœa is that of a chronic diarrhœa, rather than of a dysentery. This commonly begins with mild dyspeptic symptoms, eructations, loss of appetite, etc., and a diarrhœa of moderate intensity, the stools being soft and pasty—three or four a day; the actions are often more frequent in the early morning hours. Not uncommonly, this condition is interrupted by temporary exacerbations; the attacks are sometimes dysenteric in character, the stools showing mucus and blood; in other instances more choleraic, the dejecta consisting of an abundant flux of a liquid yellowish material, while there may be vomiting, cyanosis and collapse. In many instances recovery occurs early in the course of the disease, the symptoms gradually clearing up. In other cases the patients pass on to a condition of extreme emaciation with great prostration. The anæmia is not, as a rule, very severe. Intercurrent dysentery is not uncommon and may terminate fatally.

Barbagallo (1897) and de Silvestri (1895) have reported cases in which certain nervous manifestations (headache, vertigo, tinnitus aurium, feeling of prostration) played a prominent part in the clinical picture. In de Silvestri's case there were no intestinal symptoms. All these manifestations ceased with the disappearance of the parasites under treatment with male fern.

TREATMENT.

The treatment, beyond those measures of rest and diet such as are applicable to all similar conditions, is not especially satisfactory. Normand (1877) fancied that the use of large quantities of olive oil was of a certain value purely from its mechanical action.

Perroncito (1881) believed that he had obtained results from large doses of the ethereal extract of male fern, doses as large as 12 grammes repeated daily until the disappearance of the parasite. In other instances he gave from 15-30 grammes in three doses during the morning, and repeated these daily, until the disappearance of the parasites from the stools. De Silvestri (1895) and Barbagallo (1897) in single cases, also report good results from the use of male fern. Perroncito insists particularly upon full and repeated doses, and believes that the failure to obtain good results depends upon the fact that observers have used insufficient quantities of the drug through too short a period of time.

On the other hand, Seifert (1883[2]) found that, in doses as large as 20 grammes, the ethereal extract of male fern was without effect. He obtained better results from large doses of thymol.

Grassi (1883[2]) also vigorously opposes the view that any known anthelmintic is of particular value in the treatment of this disease. This is based upon his own experience and upon the fact that adult parasites are hardly ever found in the stools even after the administration of large doses of the drugs.

Golgi and Monti (1884, 1885) and Riva (1891) also found that repeated and large doses of these anthelmintics appeared to have little or no result.

CASES.

The three cases which are here briefly reported are, I believe, the only instances which have been observed in the United States.

The first of these occurred in the Johns Hopkins Hospital nearly four years ago, and was recognized and studied by R. P. Strong, who was, at that time, a fourth-year medical student. Lieutenant Strong, who is now the director of the U. S. Army Pathological Laboratory

at Manila, has made a careful study of this case, which will be reported later by him, in the Johns Hopkins Hospital Reports.* He deserves entire credit for the discovery and recognition of the first instance of this disease noted in this country.

CASE I.—*Amœbic dysentery. Intestinal infection with* Trichomonas intestinalis *and* Strongyloides intestinalis. *Abscess of the liver. Death. Autopsy.* K., a German tailor, aged 52, was admitted to the Johns Hopkins Hospital December 7, 1896, complaining of pain and swelling in the right side of the abdomen and over the lower ribs.

The *family history* was negative.

He had had measles in childhood, but had, otherwise, been a healthy man. He denied venereal disease. Up to six years before he had lived in Austria.

Three years before entry, he began to suffer from diarrhœa which has continued since that time. There were, daily, from two to five operations, which occasionally contained a little blood; these were never associated with pain. Three weeks before entry, he began to notice a painful swelling on the right side over the lower ribs. He had had no chills, and, so far as he knew, no fever. For two weeks before entry, there had been a slight cough without expectoration.

On *physical examination* the patient appeared emaciated and feeble. The heart and lungs were negative. The abdomen was somewhat distended; there was slight movable dulness in the flanks. On the right side, over the cartilages of the tenth and eleventh ribs, there was a large fluctuating swelling, 7½ cm. in diameter; no tenderness or redness. Between this and the spinal column there was another swelling, about 15 cm. in diameter, extending from the median line to the spinous processes, and from the twelfth rib over the crest of the ilium, downward for a distance of 7 cm. The skin over this was adherent, red and thin. The hepatic flatness was not increased.

Immediately after entrance this abscess was incised and evacuated. The cavity contained a large amount of thick puriform material with dark shreds and considerable greyish debris. The cavities extended into the liver. About one and a half pints of fluid were evacuated; this contained many large, actively motile amœbæ, showing the ordinary characteristics of *Amœba coli*.

The patient had daily, from one to four fluid, brownish, foul-smelling stools, which contained, besides *Amœba coli*, considerable numbers of *Trichomonas intestinalis*, as well as numerous small nematodes identified by Mr. Strong as the rhabditiform embryos of *Strongyloides intestinalis*.† The wound and the colon were irrigated with a solution of quinine, 1/1000.

The patient gradually failed and died on December 26.

*Since the completion of this article Strong's paper has been published. (See Bibliography.)

†The conclusions of Mr. Strong were confirmed by Dr. Charles Wardell Stiles of the U. S. Bureau of Animal Industry.

The protocol of the *autopsy* reads: "Amœbic dysentery; ulceration of the large intestine; retroperitoneal abscess; operation wounds; parenchymatous and fatty degeneration of the kidneys; fatty liver; fatty heart; intestinal infection with *Trichomonas intestinalis* and *Strongyloides intestinalis*."

"The abscess cavity measured 7 x 5 cm. on the surface of the liver and extended about 4 cm. into the substance of the organ. Scrapings from the wall showed numerous amœbæ." The rectum and colon are the seat of widespread ulceration. The ulceration, which, for the most part, is shallow, leads in the rectum, into an eroded, thickened, hæmorrhagic appearance. The ulcers vary in size; the largest are irregular in shape, measuring about 3 cm. in length by 2 in width. A typical ulcer of moderate size might be described as follows: "Shallow, smooth base, somewhat striated, evidently formed by the muscular coat of the intestine; white and shining, covered with whitish shreds. The outline of the ulcer is irregular but rather clean-cut, the edges are slightly elevated and are hæmorrhagic, neither shredded nor undermined." There are a large number of small pea-sized, and smaller, yellowish, slightly elevated areas, with red margins, which on careful study, appear as shallow ulcers, filled with a tenacious yellowish material. As they grow larger, they become like the typical one described above. About the middle of the transverse colon are two perforating ulcers, rather more hæmorrhagic about the edges; the mucous membrane is turned outward. Coverslips from the ulcers show active amœbæ. The small intestine is free from ulceration; here and there is a slight ecchymotic patch. The abscess of the liver communicates with the large retroperitoneal abscess opening outward as first described.

All along the tract Mr. Strong and Dr. Stiles found embryos of *Strongyloides intestinalis*. The parthenogenetic mother worms were found in the duodenum and jejunum. Careful studies by Mr. Strong resulted in the cultivation of but one adult male of the free living generation; adult females were never found. The direct transformation of the rhabditiform embryos into the filariform larvæ was apparently the rule. A similar observation has been previously made by Grassi and Segrè (1887), who found that, when the direct transformation predominated, the sexually differentiated forms found in the cultures were always males.

The point of origin of the infection in this case was not apparent. The disease may have been brought from Austria. The patient lived in the city, and drank city water.

CASE II.—*Chronic diarrhœa. Rhabditiform embryos of* Strongyloides intestinalis *in the dejecta. Great improvement.*

N. P., a boy seventeen years old, presented himself at the dispensary of the Johns Hopkins Hospital May 10, 1899, complaining of diarrhœa.

The *family history* was good. There was no history of pulmonary trouble or of hereditary disease. The grandmother, however, had suffered from diarrhœa for five years.

Personal History.—The patient had lived all his life in Richmond, Virginia, where he had been a newsboy. He had had measles, whooping cough and mumps as a child, and had suffered, off and on, from indefinite pains in both legs. Five years before entry, he had tertian ague. There was no history of pneumonia, typhoid fever, acute rheumatism, pleurisy, scarlet fever or chorea.

Present Illness.—Three years before entry, the patient began to suffer from diarrhœa, the attack coming on during the summer. The operations were very thin and yellowish in color, containing at times, a small amount of blood, though this had not been noticed for a year and a half. The passages occurred mainly at night, as many as seven or eight in twenty-four hours, but of late, only about four. There was, at first, considerable mucus in the stools, but this had been practically absent during the two years before entry. The diarrhœa had never been associated with pain. The patient, however, had grown gradually weaker, and during the second year of his illness, he had been compelled, on one occasion, to take to bed for two weeks. Four months before entry, he gave up work on account of weakness, though up to that time he had felt tolerably well.

The appetite was good; there were no dyspeptic symptoms.

Physical examination showed a slight, emaciated boy, of sallow color. The lips and mucous membranes were somewhat pale; tongue clean. The chest was long and narrow; the intercostal spaces, deep. Examination of the heart and lungs was negative. The abdomen was not distended. The spleen was not palpable. No peristaltic movements were visible. There was no enlargement of the liver; no glandular enlargements; no scars upon the shins. There was an irregular chloasma-like pigmentation over the cheeks, forehead and temples, and also over the lower thorax and lateral abdominal regions.

The *urine* showed no abnormalities.

The *blood* showed no marked leucocytosis; no apparent increase in the eosinophilic cells.

A rectal tube was introduced and a little, brownish, foul-smelling material was obtained which, besides muscle fibres, vegetable cells, granular debris and bacteria, contained a number of actively motile worms. In the fresh stools these measured all the way from 0.225 to 0.45 mm. in length by 0.02 to 0.03 mm. in breadth. They showed the characteristic structure of the rhabditiform embryos of *Strongyloides intestinalis*, and manifested a very active serpentine motion.

The worm diminished slightly in size toward the head, and gradually tapered down to a slender sharp-pointed tail. The periphery was somewhat refractive, while within, the substance was filled

with glistening, refractive, fat-like granules, which were rather larger toward the head than toward the tail. The digestive tract was clearly visible. The œsophagus, between one-third and one-fourth the length of the worm, showed a long bulb-like enlargement at the head, followed by a constriction, which was succeeded by a second, round or ovoid enlargement. The digestive canal was readily seen to pass through these enlargements, the anal outlet being situated at a distance equalling about one-tenth the length of the worm from the tip of the tail. The anterior lip of the anal outlet was slightly raised. The mouth of the worm appeared, as far as could be made out, to consist of a simple funnel-shaped depression. In some instances the lumen of the digestive canal appeared to pass, as a straight line, directly through the œsophageal enlargements. In others, a distinct triangular opening was to be seen in the middle of the second of the œsophageal enlargements; the outlines of this opening were glistening and refractive, indicating clearly the tridentate, chitinous armature described by other observers (Plate IX, Fig. B). In many of the active worms repeated and violent muscular contractions of the œsophagus were observed; these were especially marked about this tridentate opening, which appeared to open and shut with considerable force. The outlines of the cells bordering the digestive tract, of which, in some instances, a slight suggestion could be made out, were as a rule entirely hidden by the glistening granules above mentioned. A little below the middle of the worm, on the same side as the anal opening, was a small clear elliptical area—the rudiment of the sexual apparatus.

The boy refused to enter the hospital, and was observed in the out-patient department off and on up to June 21. As far as possible he was kept in bed, placed upon a liquid diet and given large doses of bismuth. On May 21 he was given santonin 0.25 (gr. IV) followed by castor oil, but no adult worms were found in the discharges. He was also given high rectal irrigations with a 1/2500 solution of quinine; on several occasions thymol was administered, a dose of 2. (gr. XXX) being given on successive hours, followed by a castor oil purge.

The diarrhœa gradually diminished and the stools became semi-solid in character, but still contained parasites.

No adult forms of the worm were ever found. The parasites always died a few hours after the stools were obtained, possibly owing to the fact that urine was mixed with the dejections.

On June 21, the patient went home, but returned to the hospital on July 7. He was immediately put to bed, and given a liquid diet.

The stools, at this period, were from three to four in number in the twenty-four hours. They were at first of a pea-soup consistency, having a peculiar, foul smell, and showing considerable numbers of the rhabditiform embryos.

For a time the only medicinal treatment consisted of large doses of bismuth.

The stools were collected, free from the urine, and various culture experiments were made. In some instances the fæces were placed in the thermostat and kept at body temperature. In others, they were kept near the thermostat at a temperature of about 30-35° C. Other specimens were kept at room temperature, 20-30° C. When but few parasites were present, the method suggested by Leichtenstern (1898) was followed. In the semi-solid or solid fæces an excavation was made into which a little water was poured. Some hours later considerable numbers of parasites were usually to be found in this fluid. The best results were obtained in those cultures made at a temperature of 30-35° C.

The smallest worms, found immediately after the passage, measured about 0.22 mm. in length. During the next several hours they were observed to grow considerably until the largest measured about 0.55. Within twelve hours the greater number of the worms in the cultures had lost the distinct œsophageal enlargements, and had become somewhat longer and more delicate in structure, measuring usually from 0.4 to 0.55 mm. in length and, in one recorded instance, as much as 0.7 mm. Sometimes examples were found measuring under 0.4 mm. The transverse measurement was from 0.016 to 0.022 mm. All trace of the rudiment of the sexual gland disappeared. The anal opening was not evident and the digestive tract was visible

only through about half the length of the worm. In the posterior half of the worm the granules were darker and apparently more abundant than in the anterior portion. Though the parasite, as a whole, was more delicate than the younger embryo, the tail, as shown in the drawing (Plate IX, Fig. C), was blunter, and more truncated.* The parasites became rather more active, showing most striking serpentine movements, the appearance coinciding entirely with that of the filariform larvæ of *Strongyloides intestinalis.*

Though the stools were carefully studied during the patient's entire stay in the hospital from July 7th to August 26th, and though cultures were made daily, no examples of the sexually differentiated, free living generation were found.

In many of the specimens, worms were seen in which the outer layer had the appearance of a refractive capsule, but no constant relation between this appearance and the development of the parasite was traced. The moulting or escape of the parasite from this capsule was not observed.

In one or two instances the worm was noted, under observation, to become suddenly motionless, while the capsule became shrunken and greatly wrinkled. The finer points in the internal structure of the worm were no longer to be made out.

Although, as has been noted, the stools were examined several times a day through a long period of time, only two eggs were observed. These were similar in appearance. Drawings and measurements were made of one seen on the twenty-fifth of May.

These eggs were of elliptical shape, with a thin, clear, yellowish shell, and granular contents which could be clearly seen to be in segmentation. The measurements were about 0.0675 by 0.0375 mm. The appearances have been admirably reproduced by Broedel in Plate IX, Fig. A.

The condition of the patient improved greatly during his stay in the hospital. During the greater part of the time, he received subnitrate of bismuth 1.3 grm. (grains XX) three times a day. On several occasions thy-

* The truncation of the tail was not noted in the detailed observations, which were made before a careful study of the literature was undertaken. In the admirable drawings, however, made from life by Broedel, this point is clearly brought out.

mol was given, in two doses of 2. (gr. XXX) each, and on July 28 the patient took two doses, separated by an interval of an hour, of 4. (℥i) each, of fluid extract of male fern, followed by a purge. Neither eggs nor mother worms were found in the stools. The stools gradually became more solid, though never formed; they diminished in frequency until, finally, there were only one or two in the twenty-four hours. The diet was gradually increased, and, on July 24, he was allowed the regular ward diet. On August 26 the patient was, at his own request, discharged; he had gained twenty-two and one-half pounds in weight. On discharge, however, the pasty stools still showed moderate numbers of the rhabditiform embryos. Through friends of the patient it has been learned that he has, since this time, regained his normal weight and strength. He has resumed his occupation and considers himself well.

CASE III.—*Arterio-sclerosis. Chronic diarrhœa. Embryos of* Strongyloides intestinalis *in the dejecta. Secondary anæmia. Great improvement.*

J. S., a farmer, a native of Anne Arundel County, Maryland, was admitted to the Johns Hopkins Hospital July 19, 1900, complaining of diarrhœa and swelling of the feet.

Family history, good.

Personal History.—The patient had been a farmer all his life; his habits had been good; he had had no serious illnesses, excepting chills and fever fifteen years before entry. He had always lived in Anne Arundel County, having never been out of the State of Maryland, excepting for occasional visits to Washington.

Present Illness.—He had considered himself a healthy man up to six months ago when he began to suffer from diarrhœa and progressive weakness. The stools, very frequent and sometimes involuntary, were fluid but never contained blood. They were small in quantity. During two months before entry, the patient had, on several occasions, vomited a yellowish fluid. For two days he had had sharp, griping pains in the lower abdomen. For a month there had been œdema of the feet and legs.

There had been no increase in the quantity of urine, though there was increased frequency of micturition. During the last two months he had lost considerably in weight and much in strength.

The examination by Dr. Futcher, on January 20, showed a rather sparely nourished man with a sallow complexion; moderate thickening of the radial arteries; no arcus senilis. Physical examination of the lungs was negative. Heart sounds, feeble, but free from murmurs. The abdomen was slightly full, bulging in the flanks, everywhere flat excepting in the umbilical region, where there was tympany; hepatic flatness, continuous with the abdominal flatness.

On July 19, a count of the leucocytes showed 21,500 to the cubic millimetre. Rectal examination showed numerous external hæmorrhoids; the mucous membrane felt rather soft; the prostate was enlarged and firm.

The *dejecta* were fluid, containing considerable pus, great numbers of leucocytes, a few red blood corpuscles and a moderate number of characteristic rhabditiform embryos of *Strongyloides intestinalis*.

The *urine* showed, throughout, a rather low specific gravity, 1005-1015, a trace of albumin, and occasional hyaline and granular casts. The quantity was not accurately estimated.

The temperature was slightly elevated, 100.6°, on entry, but, with the exception of an occasional rise to a point between 99° and 100°, it remained sub-normal during the greater part of the patient's sojourn in the hospital.

On July 26, a blood count showed: Red blood corpuscles 3,560,000; hæmoglobin 57%.

On entry the patient was given a milk diet, and powders containing: Tannogen 0.65 grm. (grains X), bismuth. subnit. 2. (gr. XXX) every four hours; also diuretin, citrate of potassium and strychnine. On the following day, the medicines, with the exception of the strychnine, were omitted.

On the 24th, tannogen 0.65 (gr. X) every four hours, was again ordered, as well as diuretin 0.325 (gr. V) every four hours.

There was little improvement in the condition of the patient up to August 12, on which date he was given thymol 0.325 (gr. V) every four hours, which resulted in an apparent improvement for about two weeks, after which time the diarrhœa returned. On August 21 the tannogen was discontinued, and the patient was given subnitrate of bismuth 1.3 (gr. XX) every four hours. On August 31 the bismuth was omitted and the tannogen was discontinued again September 4, and salol 0.325 (gr. V) every four hours was ordered. On August 13, the thymol was discontinued and four doses of santonin were given at hourly intervals without any striking results. The number of movements, however, became somewhat reduced and the general condition of the patient was considerably better. There was a gain of twenty-one and a half pounds in weight between July 29 and September 17, the date of his discharge.

Cultures from the fæces, made according to the same methods as in the last case, showed the direct transformation of the rhabditiform embryos into the filariform larvæ; the change was complete, in many instances, within twelve hours. No adult forms of the sexually differentiated, free-living generation were observed. No eggs were found in the stools, nor were any examples observed of the parthenogenetic mother worm.

These three cases are interesting in that they are the first which have been observed in this country. Of especial importance is the question regarding their point of origin. In the first case it is possible, though scarcely probable, that the disease may have been acquired in Austria. In the second and third, however, the disease must have originated here.

The behavior of the parasite on culture was similar to that commonly observed in cases arising in temperate climates. In all three cases, the direct transformation of the rhabditiform embryos into the filariform larvæ predominated. In one instance only, was a single

sexually differentiated form of the intermediate, free generation observed.

Question might be raised with regard to the nature of the eggs observed in Case II. The size of the one in which measurements were made, exceeded that attributed to the eggs of the parthenogenetic mother worm by many authors. Thus, Grassi and Parona (1879) give the measurements of the eggs as 0.06 x 0.04 mm., while Braun (1895), in his manual, gives the measurements as 0.050 to 0.058 x 0.030 to 0.034 mm., and Railliet (1895) gives the same measurements. Again, most authors are unanimous in stating that the eggs are present in the stools only with the greatest rarity.

There can, however, be little doubt as to the nature of the two eggs observed in this case.

(1) In the first place it will be remembered that they were found only upon two occasions, although a careful daily search was made through several months. Moreover, all authors who have had much experience with the parasite, have noted the *occasional* presence of eggs in the fresh stools.

(2) Their general conformation agreed entirely with that of the eggs of the parthenogenetic mother worm.

(3) The measurements, though larger than those given by Grassi and Parona and in most text-books, agree, however, with those given by Golgi and Monti (1884, 1885) in their careful and accurate study, and also by Riva (1891). These observers state that the diameters vary from between 65 and 70 μ in length, by 30-39 μ in breadth.

Another objection which might be opposed to the assumption that these were eggs of *Strongyloides intestinalis*, is the fact that, in each instance, they were in the process of segmentation, and did not yet contain the completely developed embryo. Might they possibly have been the eggs of *Uncinaria duodenalis?* This can be easily ruled out, both on account of their greater size, as well as because of the fact that they were found on but two occasions. In uncinariasis the eggs are always numerous.

They could not have belonged to the sex-ripe intermediate generation; (1) because, on careful search, the adult parasites were never

found; (2) because they were found in fresh stools. It may not be impossible that these special examples may have represented eggs in which the process of development had, for some reason, been arrested.

Another question which arises in connection with this case is the following: Do these instances represent an outbreak of the disease due to parasites which have been imported within recent years, or are we to assume that this worm has long existed among us?

When one considers the infrequency with which systematic examinations of the fæces are made, it seems to me unnecessary to assume that the worm has been recently imported. It is highly desirable that, both in our hospitals and in private practice, more systematic and thorough examinations of the fæces should be undertaken than are at present customary. It is safe to say that if microscopical examination of the fæces were carried out as regularly and systematically as is the microscopical examination of the urine and the blood, a number of interesting and important observations would follow.

An especially interesting point in connection with the history of this parasite is its frequent association with *Uncinaria duodenalis*. Grassi (1879 [1]) early emphasized the frequency of combined infections, while Perroncito (1880 [1-6], 1881, 1882, 1883), Sahli (1882), and others have also brought out this fact in connection with their studies of the epidemic among the workers in the St. Gothard Tunnel. Of 30 of Grassi's autopsies in Milan in which *Anguillula intestinalis* was found, *Uncinaria* was also present in 25. Lutz (1885) in Brazil, in 35 cases of infection with this parasite, found a combined infection with *Uncinaria* in 30, or 85.7%. The conditions under which the two parasites flourish seem to be similar, and the discovery that one of the worms exists among us, should open our minds to the possibility of the presence of the other.* Especially should it emphasize the importance of a careful examination of the stools in all suspicious cases of anæmia.

* While this article is in press, Dr. John L. Yates, Assistant in Pathology, Johns Hopkins University, has discovered at autopsy a case of Uncinariasis (Anchylostomiasis) at the Baltimore City Asylum at Bay View.

The relation of the parasite to the diarrhœa in these three instances is somewhat questionable. In Case I, the exciting cause of the process is uncertain, the parasite having been associated with *Amœba coli*. In Cases II and III, however, there was no apparent cause for the diarrhœa other than the presence of these nematodes. And while, in both instances, the parasites were present upon the discharge of the patient, improvement was associated with a great reduction in their number.

In conclusion one may be justified in emphasizing the following points:

(1) Diarrhœa associated with the presence of *Strongyloides intestinalis* occurs in the United States.

(2) The observation, in the Johns Hopkins Hospital, of three cases within three years, cases originating probably in Maryland and Virginia, suggests that this parasite may be more frequent than has hitherto been supposed.

(3) As in most cases originating elsewhere, in temperate climates, the development of the sexually differentiated, free living generation was in these instances apparently unusual, the direct transformation of the rhabditiform embryos into filariform larvæ predominating.

(4) The discovery of the existence of *Strongyloides intestinalis* should emphasize the possibility that *Uncinaria duodenalis* may also occur in this country.

(5) More systematic examinations of the fæces both in public clinics and in private practice are much to be desired.

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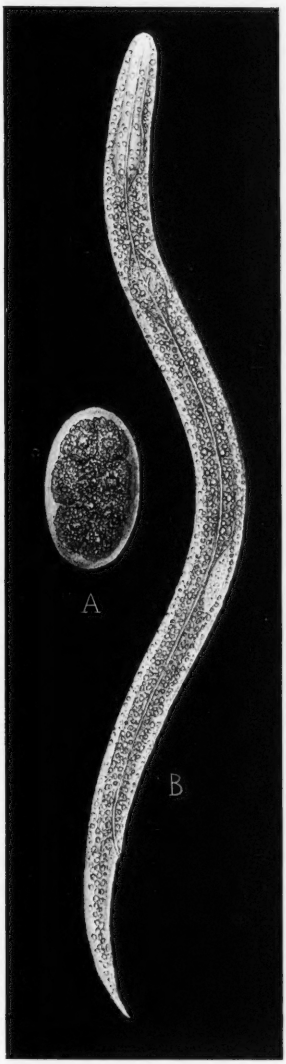
DESCRIPTION OF PLATE IX.

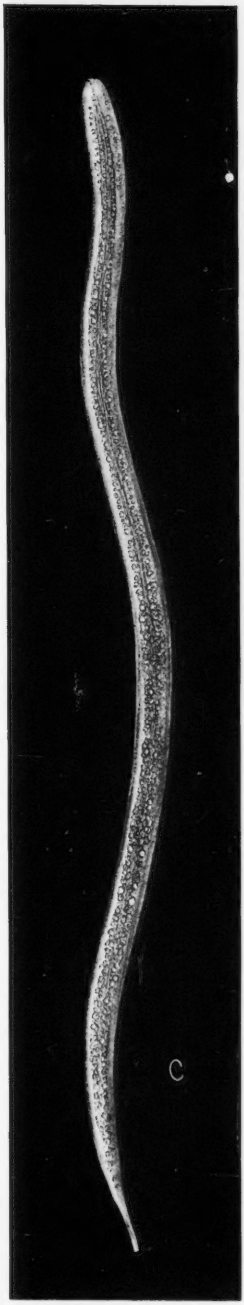
These figures were drawn from life by Max Broedel, Leitz, Objective 7, Ocular 3.

A. Egg of *Strongyloides intestinalis* (parasitic mother worm) found in stools of Case II, on May 25, 1899.

B. Rhabditiform embryo of *Strongyloides intestinalis* from the stools.

C. Filariform larva of *Strongyloides intestinalis* derived, by direct transformation, from a rhabditiform embryo.


A
B


C